EFFECT OF DIABETIC CONTROL ON GLYCOSYLATED HEMOGLOBIN AND HIGH-DENSITY LIPOPROTEIN LEVELS

by

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A thesis submitted to the faculty of
The University of Utah
in partial fulfillment of the requirements for the degree of

Master of Science

College of Nursing

The University of Utah

March 1982

THE UNIVERSITY OF UTAH GRADUATE SCHOOL

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ABSTRACT

This study investigated the relationship between diabetic control and heart disease risk in diabetic subjects. Glycosylated hemoglobin (Hb Alc) and high-density lipoprotein (HDL) levels were used as control and risk indicators. The purpose of the study was to describe the relationship between indicators of diabetic control and heart disease risk in diabetic subjects using conventional insulin injections and those same indicators when the subjects were receiving continuous subcutaneous insulin infusion from a portable battery-powered pump.

The study described changes in glycosylated hemoglobin (Hb Alc), high-density lipoprotein (HDL), cholesterol, and triglyceride levels during a control and experimental period each lasting six and three continuous months respectively. During the control period, the subjects continued to use conventional insulin injections. Within the first and final week of the six month control period, Hb Alc, HDL, cholesterol and triglyceride levels were measured. During the first week of the three month experimental period the subjects were instructed in the operation and management of the insulin infusion pump. The subjects used the infusion pump throughout the experimental period. Levels of Hb Alc, HDL, cholesterol, and triglyceride were again measured during the final week of the experimental

period.

Descriptive analysis of relationships between Hb Alc, HDL, cholesterol, and triglyceride levels during the control and experimental periods demonstrated that diabetic control improved significantly when the subjects used the insulin infusion pump. However, the relationship between diabetic control and heart disease risk indicators -- HDL, cholesterol, and triglyceride -- was not conclusive. It was concluded that other variables were interfering with the relationship of diabetic control and heart disease risk indicators.

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ACKNOWLEDGMENTS

The author wishes to express appreciation to the Supervisory Commitee: Dr. Maeona K. Jacobs, Sandra W. Haak, M.S. and Dr. Corwin Q. Edwards, for their help and expertise in completing this investigation. Gratitude is extended to Bobbi Maire for her manuscript assistance.

The author wishes to acknowledge the loving support and continued assistance of Michael H. Hunter, Mr. and Mrs. Oscar W. Walch, and Ferne G. Hunter. Thanks is also given to Linda H. Adams for her help in editing.

CHAPTER I

REVIEW OF LITERATURE

Introduction

The prevalence of coronary atherosclerotic heart disease (CAHD) has significantly increased in the last 60 years and is now the leading cause of death in the industrialized world (Hurst, Logue, Schlant & Wenger, 1978). The relationship between heart disease and diabetes has been studied repeatedly. In the Framingham study, Steiner (1978) determined that morbidity for atherosclerotic heart disease (CAHD) in diabetics increases twofold in comparison to that in nondiabetics. Knowles (1978) reported that CAHD accounts for 71% of all deaths in diabetic patients whose diagnosis was made at age 20 or later. Current data indicates atherosclerosis proceeds more rapidly and extensively in diabetic persons than in nondiabetic persons; however, the process of atherosclerosis does not differ from nondiabetic persons (Colwell, Lopes-Virella & Halushka, 1981).

In order to explain the prevalence of CAHD in diabetic persons, certain characteristics of diabetes have been related to the acceleration and extensiveness of atherosclerosis seen in diabetic persons. These characteristics -- hyperglycemia, hypoinsulinemia and abnormal platelet activity -- can be decreased towards normal

levels with good diabetic control which mimics normal metabolism.

Evidence in the literature reveals that the continuous subcutaneous insulin infusion pump provides better diabetic control than conventional insulin injections (Pickup, Keen, Parsons, Alberti, & Rowe, 1979). The continuous infusion of small amounts of insulin with a bolus infusion before meals is similar to normal pancreatic activity and produces near normal glucose concentration.

There exist indicators for diabetic control and heart disease. The most accurate indicator for current diabetic control is the blood glucose measurement. Diabetics can measure their blood glucose level at home with a reflectance meter by using capillary blood obtained from a finger prick. The indicator for long-term diabetic control is glycosylated hemoglobin (Hb Alc) measurement which is calculated in a laboratory. The most useful indicator of heart disease risk is high-density lipoprotein (HDL) levels. High-density lipoprotein (HDL) levels correlate with the majority of commonly known heart disease risk factors. These indicators are useful to health care personnel in assessing diabetic control and heart disease risk.

The purpose of this study was to describe the relationship between diabetic control and heart disease risk in diabetic persons. This study used glycosylated hemoglobin (HbAlc) and high density lipoproteins (HDL) levels as control and risk indicators, and described relationships while the diabetics were using conventional insulin injections in comparison to results while receiving continuous subcutaneous insulin infusion by pump.

Heart Disease

Coronary atherosclerosis is a pathologic condition which is characterized by abnormal lipid and fibrous tissue accumulation in the coronary artery wall. This disrupts the vessel function and reduces the blood flow to the myocardium. When blood flow to the myocardium is reduced significantly, myocardial ischemia results. This, in turn is responsible for angina, myocardial infarction, and sudden death (Hurst et al., 1978).

Pathogenesis of Atherosclerosis

Three distinct layers make up the structure of the artery wall: the intima, media, and adventitia. The intima is bounded on the luminal side by a continuous single layer of endothelial cells. The outer boundary is a thin sheet of elastic fibers called the internal elastic lamina. Between these boundaries is an extracellular connective tissue matrix. The media is made of diagonally oriented smooth-muscle cells surrounded by collagen, small elastic fibers, and proteoglycans. The media and adventitia are separated by the external elastic lamina. The adventitia is composed of fibroblasts intermixed with smooth-muscle cells arranged between bundles of collagen and surrounded by proteoglycans (Ross & Glomset, 1976).

Lipids are transported in the circulation. Proteins or polypeptides, known as apoproteins, perform the function of lipid carriers since lipids are insoluble in water. The lipids and apoproteins are known as lipoproteins. Four types of lipoproteins

have been identified: a) Chylomicrons; b) very-low-density lipoproteins (VLDL); c) low-density lipoproteins (LDL); d) high-density lipoproteins (HDL). The LDL has the greatest atherogenic potential due to its ability to deposit lipids into arterial wall cells. The HDL has the least atherogenic effect (Hurst et al., 1978).

Ross and Glomset (1976) have suggested a current common hypothesis concerning the pathogenesis of atherosclerosis. The basis of their hypothesis lies in the similarity between atherosclerosis and arterial response to experimental injury.

The atherosclerotic lesion starts with an injury to the endothelium of the artery. For example, hypercholesterolemia or hypertension can injure the endothelium and cause desquamation. Injury to the endothelium causes an immediate platelet response. Platelets adhere to the subendothelial connective tissue at the site of injury. Once they adhere, the platelets aggregate and lose the contents of their granules into the artery wall. These platelet factors interact with plasma constitutents in the artery wall. One of these factors is mitogen, which stimulates focal proliferation of arterial smooth muscle cells. Smooth muscle-cells migrate from the media into the intima by going through the fenestrae, or openings, of the internal elastic lamina. These cells then multiply, causing the intima to thicken rapidly. The proliferative cells are soon surrounded by newly formed collagen, elastic fibers, and proteoglycans.

As the lesion progresses, lipids are deposited within the proliferative cells and their surrounding connective tissue matrix.

Arterial extracellular matrix in culture forms glycosaminoglycan. Because glycosaminoglycan has an increased affinity to bind with low-density lipoproteins (LDL), it is believed that they may have an important role in the deposition of lipids during lesion formation (Ross & Glomset, 1976).

During the smooth-muscle cell proliferation and lipid deposition, the endothelial cells attempt to regenerate and recover the exposed intima. Restoration of the endothelium ultimately occurs and the lesion regresses if the injury is limited. This leaves only a slightly thickened intimal layer which contains only a few new layers of smooth-muscle cells.

However, if the injury to the endothelium is continuous or repeated, there is further proliferation of smooth-muscle cells, accumulation of connective tissue, and deposition of lipids. This will eventually form a fibrous cap or plaque. If the fibrous plaque becomes altered as a result of hemorrhage, calcification, cell necrosis, or mural thrombosis, it becomes a complicated lesion. This complicated lesion is often associated with occlusive artery disease (Ross & Glomset, 1976; Colwell et al., 1981).

In review, the sequence of events in atherosclerosis is: endothelial injury, platelet adhesion, platelet aggregation, plasma permeation of arterial wall, smooth-muscle cell migration and proliferation, extra-cellular matrix (connective tissue) formation, and extra-cellular and intra-cellular lipid accumulation.

Heart Disease Risk

Epidemiological studies have revealed certain risk factors which are associated with CAHD. These factors are age, sex, familial history, elevated serum lipid levels, diet, hypertension, smoking, diabetes, obesity, sedentary living, and psychosocial tension. The presence of one risk factor does not give predictability of the occurrence or severity of CAHD. It has been recognized, however, that the presence, of two, three, or four risk factors has a progressive and synergistic effect of CAHD risk (Hurst et al., 1978).

Recent studies in atherosclerosis research have focused on high-density lipoproteins (HDL) as a predictive risk factor (Hulley, Cohen & Widdowson, 1977; Miller, Thelle, Førde & Mjøs, 1977; Castelli, Doyle & Gordon, 1977; Van Gent, VanDerVoort & Hessel, 1978; Francis, 1980). A strong inverse correlation between plasma HDL and CAHD has been established.

Miller and Miller (1975) postulated two mechanisms by which HDL may slow the atherogenic process:

1. HDL may facilitate cholesterol transport from the arterial wall cell.

2. HDL may inhibit the uptake of cholesterol by inhibiting intake of LDL by arterial wall cells. Their study demonstrated a strong inverse relationship between plasma HDL concentration and the size of the body's cholesterol pool. This suggests that HDL limits the accumulation of cholesterol in arterial cells (Miller & Miller, 1975).

Carew, Hayes, Koschinsky and Steinberg (1976) reported that

HDL binds to the surface of porcine arterial smooth-muscle cells as effectively as LDL but is internalized and degraded much more slowly, thus inhibiting the uptake and degradation of LDL. They also discovered that HDL suppresses the net amount of cell sterol content induced by LDL. Speculatively, a low HDL concentration leads to defective clearance of cholesterol and cell saturation, thereby accelerating the development of atherosclerosis. An increased HDL concentration seems to have a protective effect in that cholesterol clearance is more efficient.

HDL and Established Risk Factors

Age. In the Tromsø Heart Study report, Mjøs, Thelle, Førde & Vik-Mo (1977) reported changes in HDL levels with age. In females, 0-49 years, the HDL cholesterol rose slightly, but not significantly with age. The HDL levels did not change significantly in increasing age in males either. Martin, Haskell and Wood (1977) in their study of distance runners in California reported that HDL cholesterol increased with increasing age in active runners while controls showed a slight decrease or no change in HDL with increasing age.

The development of atherosclerosis is dependent on time; thus a consistent relationship between age and CAHD depends on the accompaniment of other risk factors.

Sex. Barr, Russ, and Eder (1951) observed that during the reproductive years women have decreased susceptibility to CAHD in relation to men. Women have substantially higher levels of HDL than men until age 50. From age 50 to age 80 there is a slight

decrease in HDL levels in women toward the male values (Gordon, Castelli, Hjortland, Kannel, & Dawber, 1977). These findings contribute to an understanding of why men are more prone to develop atherosclerosis than women until the age of menopause; after age 50, there is decreased sex difference in the incidence of atherosclerosis.

Family History. The Framingham Study revealed that the children of coronary heart disease patients had lower HDL levels than children of healthy parents (Miller et al., 1977). The Tromsø Heart Study discovered a positive correlation in pairs of family members involving the mother and sib-sib pairs of the same sex, suggesting that intrafamilial resemblance in HDL levels is sex-associated (Mjøs et al., 1977). Other studies have confirmed that an individual with either parents or siblings affected by CAHD prior to age 50 has a greater risk of developing the disease at a younger age (Hurst et al., 1978). Although familial tendency may be influenced by genetic transmission, other environmental factors inherent in family life should also be appraised. These factors included nutrition, socioeconomic level, and activity patterns.

Elevated Lipid Levels. Hypercholesterolemia and hypertriglyceridemia have been topics of interest for several years. The risk of atherosclerosis increases with high cholesterol levels. Most of the cholesterol in the body exists as LDL, and as LDL levels increase, HDL levels decrease. Therefore, a person with hypercholesterolemia has a lower HDL level (Miller & Miller, 1975).

There may also exist an increased risk of atherosclerosis with

hypertriglyceridemia. Plasma triglyceride exists predominantly as a component of VLDL. A negative correlation between VLDL and HDL has been reported (Miller & Miller, 1975). This is the same correlation that exists between LDL and HDL. An explanation for this is that VLDL is a precursor of LDL (Colwell et al., 1981). These results coincide with previous results of strong correlations between hypercholesterolemia, hypertriglyceridemia, and CAHD.

Diet. A diet rich in calories, saturated fat, and cholesterol is associated with increased CAHD risk. Hulley et al. (1977) report that there was an increase in HDL levels in those participants who adhered "well" to a diet designed to lower total serum cholesterol concentration. For those whose adherence was judged "fair" or "poor," there was little change in HDL levels.

Hypertension. There is a significant association between hypertension and CAHD. However, epidemiologic studies suggest that hypertension accelerates atherosclerosis only when hyperlipidemia is present. When hyperlipidemia is present, the effect of hypertension is related to the extent of lipid abnormality (Hurst et al., 1978). The Tromsø Heart Study concluded there was no significant difference in HDL levels between case and control groups with hypertension (Miller et al., 1977). The relationship between HDL and lipid abnormalities has been discussed previously.

Smoking. The effect of smoking, as a risk factor, is proportional to the number of cigarettes smoked per day. The risk of developing CAHD increases two to six times for smokers as compared to nonsmokers (Hurst et al., 1978). Pozner and Billimoria (1979)

observed that LDL and VLDL levels were significantly increased with heavy smoking. A decrease in HDL levels was also observed, although it was not significant.

Diabetes. Diabetics tend to develop a greater number of atherosclerotic lesions, more extensive lesions, and more significant lesions at an earlier age. Calvert et al. (1978) found low HDL levels in diabetics who had a high hemoglobin Alc (HbAlc) level, which is a measurement of diabetic control.

Obesity. The degree of obesity determines the amount of atherosclerotic risk. Obese people frequently develop hypertension, diabetes, and hyperlipidemia, thus increasing their risk for CAHD. There is a strong inverse correlation between weight and HDL levels (Gordon et al., 1977).

Sedentary Living. Sedentary living enhances the probability of CAHD. In contrast, increased activity can actually decrease other risk factors, such as obesity, hypertension, hyperlipidemia, and psychosocial tension. Also, very active persons are found to have increased HDL levels (Lehtonen & Viikari, 1978). Therefore, people with a sedentary lifestyle would be expected to have low HDL levels.

Psychosocial Tension. Psychosocial tension or personality type and CAHD have consistently been associated in epidemiological studies of industrialized countries. Anxiety has been shown to increase serum cholesterol and increase the tendency for hypertension. Nevertheless, exact relationships of stress and CAHD have been difficult to prove since there are no satisfactory

available methods to measure degrees of stress. No present research study has attempted to relate HDL levels with stress, although the increase in serum cholesterol would be similar to hypercholesterolemia previously mentioned (Francis, 1980).

In summary, HDL levels have an inverse relationship with eight of the established eleven risk factors. Levels of HDL do not change significantly with age or hypertension. Studies of the relationship between HDL and psychosocial tension have not been reported. The Tromsø Heart Study reported that low HDL levels are a common antecedent of clinical CAHD and do not merely follow its onset as a consequence. In the eight variables studied, HDL levels made the most important independent contribution to the prediction of future CAHD in young men, with coronary risk increasing with decreasing HDL levels. An individual could be predicted as likely or unlikely to develop CAHD with 85% accuracy during the two-year follow-up (Miller et al., 1977). This demonstrates the importance of measuring HDL levels in calculating CAHD risk.

Diabetes and Heart Disease

Before the discovery of insulin, people with diabetes mellitus died from infections and diabetic coma; now they die of cardiovascular diseases (Zdanov & Vihert, 1976). The relationship between diabetes and heart disease has been established. It is believed that the inherent characteristics of the diabetic state accelerate the atherosclerotic process.

Diabetic Characteristics

Insulin and Glycemia. Insulin-dependent diabetics use exogenous insulin to maintain normoglycemia. This insulin is administered by single or multiple injections of one or more insulin preparations. Insulin preparations have onset times ranging from one half to eight hours, peak action times (when greatest amounts are in the circulation) spanning between two and twenty-four hours, and duration of action times ranging between eight to thirty-six hours. Each insulin administration results in insulin-level fluctuations of hypoinsulinemia, normoinsulinemia and hyperinsulinemia which are related to the given insulins onset, peak action, and duration of action times. Hypoinsulinemia also occurs when the diabetic's insulin requirement increases, such as during illness, infection, trauma or surgery. Hyperinsulinemia develops when there is a delay or omission of a meal, increased exercise, or an error in measurement resulting in excess dosage (Beland & Passos, 1981; Luckman & Sorensen, 1980).

Both hyperinsulinemia and hypoinsulinemia can cause hypertriglyceridemia. Hyperinsulinemia, or an excessive amount of insulin bathing the liver, is directly related to an increased rate of VLDL triglyceride production. Hypoinsulinemia increases the mobilization of stored triglyceride from adipose tissue in addition to decreasing the uptake of triglyceride by adipose tissue. Hypoinsulinemia also inhibits lipoprotein lipase activity which regulates the removal of circulating triglycerides (Steiner, 1978). The majority of triglycerides are transported by VLDL in the circulation. Very

low-density-lipoproteins provides a substrate for hepatic production of LDL which is the major contributor to cholesterol accumulation in the intima (Colwell et al., 1981). As a result, both hyperinsulinemia and hypoinsulinemia indirectly cause increased LDL. As LDL levels increase, HDL levels decrease (Miller & Miller, 1975).

Hypoinsulinemia results in hyperglycemia. During hyperglycemia the uptake of glucose is not limited in the lens of the eye, Schwann cells in nervous tissue, and in the artery wall. Within these cells, glucose is converted to sorbitol by the enzyme aldose reductase and follows the "polyol pathway." Sorbitol is not freely diffusible across the cell membrane, and so it remains in the cell where it is metabolized slowly. The accumulation of sorbitol intracellularly precipitates osmosis and consequent swelling of the cell. This produces electrolyte alterations, loss of sodium pump activity, and altered cellular metabolism (Skyler, 1978).

Abnormalities in Platelet Activity. Abnormalities in platelet activity have also been noted in diabetes. Platelet adhesiveness and aggregation are increased. Colwell et al. (1978, 1981) reported a relationship between the increased platelet adhesiveness in diabetics and the decreased platelet adhesiveness in patients with von Willebrand's Disease. For patients with von Willebrand's Disease, normal platelet adhesiveness can be restored by the addition of factor VIIIR: WF, a glycoprotein which is found in large quantities in cryoprecipitate. The relationship was further demonstrated in pigs that were markedly deficient in factor VIIIR: WF; atherosclerosis could not be induced to advanced stages even with

forced fat feeding. Therefore, they concluded that elevated factor VIIIR: WF levels in diabetes contribute to increased platelet adhesiveness.

Hypersensitivity to aggregating agents, such as ADP, epinephrine or collagen, can be shown in platelet-rich plasma of diabetics. Platelet release of granules or aggregation at low concentrations of these agents can be suppressed in diabetics by prostaglandin synthetase inhibitors. If the prostaglandin synthetase is not inhibited, platelets become hypersensitive to aggregating agents. Thus, increased prostaglandin synthetase activity appears to be present in platelets from diabetics (Colwell, 1978).

Diabetic Factors and Atherosclerosis

The inherent characteristics of diabetes have been identified as hypoinsulinemia, hyperinsulinemia, hyperglycemia, and increased platelet adhesiveness and aggregation. Each of these will be related to the pathogenesis of atherosclerosis as described in the previous section. For review, the sequence in events of atherosclerosis is: endothelial injury, platelet adhesion and aggregation, smooth-muscle cell migration and proliferation, extracellular matrix formation, and lipid accumulation.

Endothelial Injury. Hyperglycemia can cause endothelial injury (Colwell, 1978). The endothelial cells of the artery do not limit glucose transport into the cell. These cells contain aldose reductase, which causes the glucose to enter the polyol pathway. This pathway, the accumulation of sorbitol and water, causes the

cell to swell, thus altering normal function. Endothelial injury follows any significant swelling. Therefore, the prevalence of coronary atherosclerosis is higher in the presence of hyperglycemia. This association is independent of serum cholesterol and blood pressure levels (Epstein, 1967).

Platelet Adhesion. Platelet adhesion occurs in response to endothelial injury. In a diabetic person whose platelet adhesiveness is increased, greater numbers of platelets adhere to the site of injury and come in contact with aggregating agents.

Platelet Aggregation. Platelet aggregation is increased due to the hypersensitivity of platelets to aggregating agents. The increased adhesiveness and aggregation act in concert to enhance and facilitate the following events in atherosclerosis.

Smooth-Muscle Cell Migration and Proliferation. Smooth-muscle cell migration and proliferation are stimulated by platelet factors as a result of platelet aggregation. The migration and proliferation are further accelerated by the presence of insulin (Colwell et al., 1981). During periods of hyperinsulinemia, this produces larger amounts of connective tissue matrix formation and intimal thickening.

Lipid Accumulation. Extracellular and intracellular lipid accumulation is dependent upon the amount of lipids in the blood and the binding capacity of the proliferative cells. Insulin increases the lipoprotein uptake in the arterial smooth-muscle cells and directly affects the arterial wall lipid metabolism leading to lipid accumulation (Bierman & Brunzell, 1978). Hyperlipidemia is

the result of hyperinsulinemia and hypoinsulinemia; thus lipid accumulation is more extensive and greater as fluctuations in insulin concentration occur.

The effect of diabetic factors in each event of the atherosclerotic process has been identified, accounting for the fact that atherosclerosis proceeds more rapidly and extensively in diabetic persons.

Diabetic Control

Diabetic control is characterized by normoglycemia. The failure to maintain normoglycemia in diabetics is largely due to the inability of subcutaneously administered exogenous insulin to mimic the pattern of insulinemia in nondiabetics. When normoglycemia and normal insulinemia cannot be maintained, the diabetic factors of hypoinsulinemia, hyperinsulinemia and hyperglycemia ensue (Service & Nelson, 1980). The effect of diabetic control on platelet function is unclear. However, some studies have demonstrated that when severe hyperglycemia is corrected with insulin therapy, the enhanced platelet aggregation response is decreased (Peterson, Forhan & Jones, 1980; Colwell et al., 1981). Since diabetic control can decrease these diabetic factors, and these factors are directly related to atherosclerosis, then diabetic control could decrease and possibly prevent atherosclerosis in diabetic persons.

Diabetic Control Tests

Management of diabetic control requires measurement of glucose to guide insulin therapy. Glucose measurements can be made from urine and from blood specimens.

Urinalysis. The advantages of testing urine for glucose are low cost, lack of body invasion, and avoidance of pain. The major disadvantage is that urine test results may be misleading. Urine glucose is often high with concurrent normoglycemia. This is commonly due to incomplete voiding of glucose-positive urine in the bladder before the second voided specimen. Urine glucose measurement will not indicate hyperglycemia if the diabetic person has high renal threshold of glucose clearance, diminished glomerular filtration rate, or increased tubular reabsorption of filtered glucose. These factors cause errors in estimating blood-glucose levels from urinalysis, making diabetic control assessment more difficult (Danowski, Ohlse, Fisher, & Sunder, 1980).

Blood Glucose. Blood glucose measurements are accurate but only reflect diabetic control at the time the blood sample is obtained. Blood glucose may be measured in the physician's office or hospital laboratory, or at home by the diabetic person. Home analysis of blood glucose may be done with a glucose-oxidase reagent strip and reflectance meter which requires a "finger stick" blood sample. In the majority of diabetics who monitor blood glucose levels as a guide to multiple injections of insulin, diabetic control is improved (Danowski et al., 1980).

Peterson et al. (1980) reported that their diabetic patients had greater compliance and better diabetic control when they monitored their blood glucose with reflectance meters before and after meals. Glucose measurement by reflectance meter correlated with laboratory measurement of glucose with a correlation coefficient

between 0.92 and 0.97. The same correlation existed with all three meters currently available on the market.

Glycosylated Hemoglobin. Glycosylated hemoglobin serves as an integrator of the mean blood glucose over several preceding weeks (Peterson et al., 1980). Hemoglobin undergoes nonenzymatic glycosylation in the presence of plasma glucose. Normally 5% of total hemoglobin is glycosylated. The covalent linkage of glucose to hemoglobin results in the formation of chromatographically distinct additional components to the hemoglobin itself. The most prevalent minor component was designated by Allen (1958) as Hb Alc according to Bunn. Interest in Hb Alc was intensified by the discovery in 1968 that there is a two- to three-fold increase in Hb Alc in patients with diabetes (Bunn, Gabbay, & Gallop, 1978).

The HbAlc is formed slowly and continuously during the 120 day life span of the erythrocyte (Bunn et al., 1978). The cumulative amount of Hb Alc is proportional to the average glucose concentration to which the erythrocyte is exposed. Gonen, Rubinstein, Rochman, Tanega & Horwitz (1977) discovered a significant positive correlation between Hb Alc and fasting glucose level, mean glucose level (several samples per day), and the highest glucose level in a day. A partial correlation coefficient showed that the Hb Alc level was mainly dependent on glucose response rather than the fasting glucose level.

Davis, Nicol, McCann and Calder (1978) recorded that in poorly controlled diabetes, diabetics have a mean Hb Alc level 50% higher than normal. After diabetic control was improved, Stanton and

Davis (1978) observed that Hb Alc levels did not decrease until three to four weeks later. He concluded that Hb Alc reaches a stable level of equilibrium after two to three months of improved control. Ditzel and Kjaergaard (1978) reported that Hb Alc levels returned to normal in twenty-five to eighty days, depending on initial Hb Alc level and blood glucose control. These data demonstrate how Hb Alc is useful in assessing diabetic control of previous months.

Relationships between Hb Alc and age, sex, duration of diabetes, and mode of treatment have been analyzed. Davis et al. (1978) obtained a significant correlation ($p < 0.01$) of Hb Alc and duration of diabetes when the diabetes was in poor control. When the diabetes was well controlled with insulin, there was no correlation with age or duration of diabetes. However, Tze, Thompson and Leichter (1978) concluded there is no correlation between Hb Alc and age, sex, or duration of diabetes.

Graf, Halter and Porte (1978) have postulated a theoretical maximum of glycosylated hemoglobin of 23.1% of total hemoglobin. Previous studies of diabetics have shown Hb Alc levels approach but do not exceed this value. Further evidence of maximum saturation level is found when, in very poorly controlled, frequently hyperglycemic diabetics, the Hb Alc levels are not elevated as high as expected. There is much evidence that Hb Alc is sensitive to moderate hyperglycemia, which in actuality is the current major problem in assessing diabetic control (Stanton & Davis, 1978). Therefore, Hb Alc is useful in assessing previous diabetic control;

however, differentiation of degrees of poor diabetic control is decreased as Hb Alc levels approach maximum values.

The urine or blood glucose test may be used by the diabetic or health-care provider to assess diabetic control. However, the blood glucose measurement is more accurate in determining normoglycemia. Blood glucose measurement with a reflectance meter is most useful for immediate diabetic control assessment. In contrast, Hb Alc is most useful in determining quantitative diabetic control over preceding weeks and months.

Diabetic Control Methods

There are four major differences between normal endogenous insulin secretion and exogenous insulin therapy. During endogenous insulin secretion, the insulin is released in a pulsatile manner in response to glucose stimulation. Thus, blood glucose and insulin levels rise and fall simultaneously. In contrast, exogenous insulin absorption is not a response to glucose stimulation but is reliant on solubility properties of the insulin and absorption rate from injection site. No homeostatic control mechanism is present in diabetic persons. Therefore, diabetic control methods should provide a balance of energy expenditure (exercise), energy availability (diet), and insulin needed for effective utilization of energy (Skyler, 1978).

Goals for the control method chosen are to: a) achieve normoglycemia; b) provide insulin in concert with meals; c) allow maximum flexibility in diet, activity, and insulin administration;

d) have maximum patient understanding and involvement in therapy. In order to obtain these goals, the optimal insulin therapy should provide peaks of insulin action at different times throughout the day. This can be produced by multiple doses of regular insulin before meals and bedtime or a split-mixed insulin regimen. This regimen splits the insulin dose between the before-breakfast and before-supper injections and mixes a short-acting and an intermediate-acting insulin for each dose. The rationale for these regimens is that they more closely mimic endogenous insulin secretion. Also, there is more flexibility in altering activity, diet, and insulin injection time. These regimens are superior to one or two insulin preparations injected before breakfast because they are less likely to precipitate hypoglycemia, hyperglycemia, hyperinsulinemia, or hypoinsulinemia at any time during the day or night (Skyler, 1978).

In the quest to achieve better diabetic control, calculated repeated doses of insulin have gained more popularity. This has led to the experimental use of continuous insulin infusion pumps. Pickup et al. (1979) observed seven insulin-dependent diabetics during 24 hours of continuous insulin infusion. Blood glucose levels and the major intermediary metabolites -- lactate, pyruvate, 3-hydroxybutyrate, alanine -- were compared to pre-pump levels and to levels in 17 nondiabetics. The mean blood-glucose level was not significantly different from that of nondiabetics. Blood concentrations of the intermediary metabolites approached those of nondiabetics, demonstrating the control that can be obtained with the

infusion pump.

Following this study, Pickup et al. (1979) investigated outpatient use of the infusion pump. Pump use was instigated in the hospital for six patients. These patients used the pump for 48 to 111 days. During this time, they monitored their diabetic control by using glucose-oxidase reagent strips with reflectance meters and managing pump operation and dosage control. The subcutaneous infusion route was used to avoid the thrombosis and infection possible with intravenous route. Cannulas were reimplanted every two to eight weeks or as necessary. During bath times, the pump was disconnected and the tubing covered with a cap. The results of this investigation were: a) statistically significant decreases in mean blood glucose for five of six subjects; b) Hb Alc decreased to normal range; c) insulin dosage decreased for five of six subjects; d) no visible or palpable inflammatory reaction or lipodystrophy; e) no micro-organisms in culture of cannula tips.

Tamborlane, Sherwin, Genel and Feliz (1979) examined lipid levels of eight patients using infusion pumps for seven to fourteen days. Plasma cholesterol, triglycerides, and free fatty acids were elevated above normal during conventional insulin therapy and decreased to normal after seven days of infusion pump use. These impressive metabolic corrections with continuous insulin infusion pumps use give a promising future to diabetic persons.

Keen, Pickup, Viberti, Bilous and Williams (1981) have described requirements for a successful infusion pump (1 to 8) and infusion pump therapy (9 to 10):

1. Reliable pump
2. Capable of basal and bolus rates
3. Small, light, robust
4. Removable
5. Controlled by diabetic
6. Simple software
7. Self-monitoring system
8. Nocturnal security system
9. Education and motivation of diabetic
10. Physician discretion.

While investigating the use of the infusion pump, Keen et al. (1981) reported that blood-glucose profiles for "brittle" diabetics were no better with pump use than that with multiple injections. He also studied metabolic response to abrupt discontinuance of insulin infusion by pump failure or by obstruction. When discontinuance occurred during waking hours, the patient perceived the change by diabetic control test results and followed recommended action. When it occurred at night, glycemia did not change for one hour, rose at a diminishing rate for the next four hours, then leveled off spontaneously. The plateau was about 4.5 mmol/L above baseline level. At the end of nine hours sleep, the subjects felt mildly unwell; however, they all recovered after resuming insulin infusion. The use of the infusion pump is becoming more common and possibilities for long-term use are increasing.

In summary, the relationship between diabetes and heart disease has been reviewed. Diabetic characteristics amplify the events

of the atherosclerotic process, although this amplification can be decreased with good diabetic control. Better diabetic control can be provided by the continuous subcutaneous insulin infusion pump than by conventional insulin injections. Assessment of long-term diabetic control and heart disease risk can be indicated by Hb Alc and HDL levels, while current diabetic control can be assessed by blood glucose levels.

There is a need for health-care personnel to understand the relationship of diabetes and heart disease. Nurses come in contact with large numbers of diabetic and CAHD patients, and thereby use their knowledge about diabetes and heart disease in clinical care and education of diabetics. In the clinical setting they relate the disease process of the client to diabetic control methods, diabetic control tests, and assessment of diabetic control and heart disease risk. In planning patient education, they require knowledge of methods to improve diabetic control and decrease heart disease risk. Therefore, an understanding of diabetes and CAHD will allow for comprehensive nursing care for diabetic and heart disease patients.

Conceptual Framework

Diabetes is a metabolic disorder resulting from insufficient insulin. Although much is known about this disease, a cure or prevention is not currently possible. Since the development of exogenous insulin, diabetic persons no longer die from ketoacidosis; instead they die from macrovascular and microvascular complications.

A major macrovascular complication of diabetes is heart disease (See Figure 1). Coronary atherosclerotic heart disease (CAHD) results from coronary atherosclerosis which decreases the blood circulation to the heart. Epidemiological studies have determined that no single factor is responsible for atherosclerosis, but multiple factors contribute to the process. These factors, recognized as risk factors, are used to determine heart disease risk. The correction or removal of the risk factors prevents or decreases the heart disease risk (Hurst et al., 1978) (See Section A, in Figure 1).

Hurst et al. (1978) have classified the risk factors as major, minor, modifiable, and nonmodifiable (See Table 1). A major risk factor is one having a high correlation with heart disease. Classification as a modifiable risk factor suggests a specific change in the diabetic state may decrease heart disease risk. Diabetes is a major modifiable risk factor (See Section B, in Figure 1).

Diabetes cannot be cured, but it can be controlled (See Section C, Figure 1). In diabetes, there is a progressive loss of glucose homeostasis which is directly proportional to the amount of insulin present. Glycemia is produced by the ingestion of food, and glucose homeostasis is obtained by the presence of insulin. Thus with insufficient insulin, as seen with diabetes, glucose homeostasis cannot be achieved. Glucose homeostasis can be restored with exogenous insulin in calculated amounts which mimic the pattern of isulinemia and glycemia in healthy persons (Service & Nelson, 1980). Therefore, normoglycemia is an

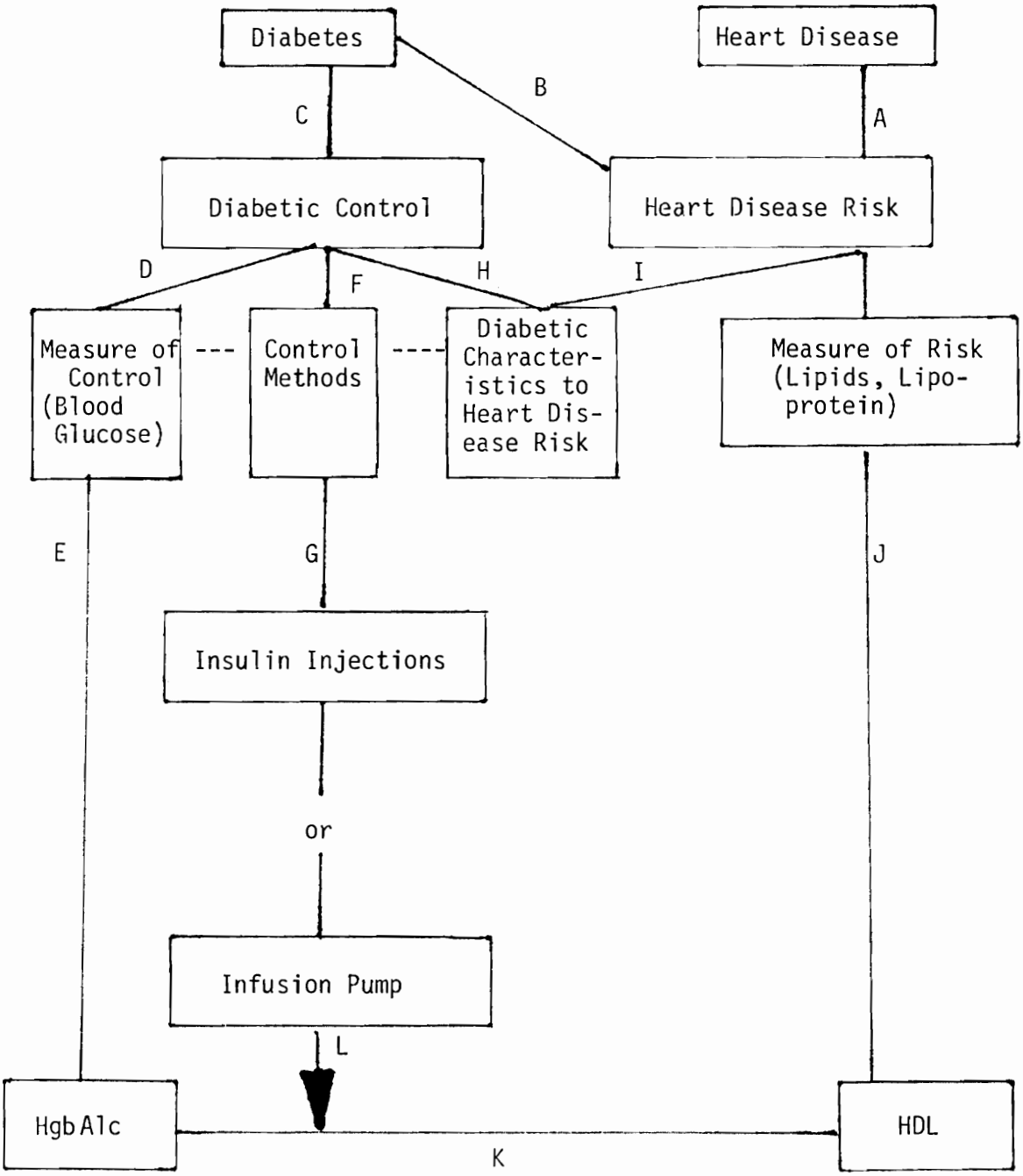

Figure 1. Conceptual framework

Table 1

Risk Factors for Coronary Atherosclerotic Heart Disease (CAHD)

Nonmodifiable Risk Factors
Age
Sex
Familial history
Modifiable Risk Factors
Major
Elevated lipid levels
Diet high in total calories, saturated fats, and cholesterol
Hypertension
Smoking
Diabetes
Obesity
Minor
Sedentary living
Personality type
Psychological stress

Note. Adapted from Hurst et al., 1978.

indication of a good diabetic control.

Several tests are available to monitor diabetic control (See Section D, Figure 1). These tests are the urinalysis, blood glucose, and glycosylated hemoglobin. The urinalysis gives an indication of blood glucose. However, it is only accurate and reliable when the renal threshold is known, as a significant relationship exists between renal threshold and glycosuria. Blood-glucose levels give an accurate assessment of diabetic control at one point in time but do not reflect previous variations. Glycosylated hemoglobin gives a quantitative assessment of diabetic control during the preceding weeks (Tattersall, Walford, Peacock, Gale & Allison, 1980) (See Section E, Figure 1). Urine glucose levels, blood glucose levels, and glycosylated hemoglobin levels increase above normal with poor diabetic control and decrease to normal range with good diabetic control. Thus, each is useful in assessing diabetic control.

Different methods are employed by diabetic persons to obtain normoglycemia or diabetic control (See Section F, Figure 1). These methods are diet, oral agents, and insulin preparations. The method which achieves the best diabetic control should be the one used by each diabetic person. Insulin-dependent diabetics inject one or a combination of insulin preparations once, twice, or more a day. Insulin is administered subcutaneously into the adipose tissue of the upper arms, thighs, buttocks, or abdomen. An innovation in insulin administration is the continuous subcutaneous insulin infusion pump (See Section G, Figure 1). Continuous infusion of

insulin with bolus amounts infused before meals duplicates insulinemia patterns of nondiabetic persons more closely than conventional insulin injections.

If the diabetic control method does not mimic the nondiabetic state, certain characteristics which are innate to diabetes develop (See Section H, Figure 1). These characteristics are hypoinsulinemia, hyperinsulinemia, hyperglycemia, and abnormal platelet activity (Colwell et al., 1981). With good diabetic control, these characteristics decrease and normal metabolism is present. If diabetic control is poor, these characteristics increase in abnormality.

Colwell et al. (1981) have reported that these diabetic characteristics -- hypoinsulinemia, hyperinsulinemia, hyperglycemia, and abnormal platelet activity -- may induce or accelerate the atherosclerosis of heart disease. Hence, if these diabetic characteristics can be decreased with good control, as previously indicated, then the heart disease risk should also decline (See Section I, Figure 1).

Since no single factor is known to be useful in calculating heart disease risk, high density lipoprotein (HDL) levels have been used (See Section J, Figure 1). High density lipoproteins (HDL) have a protective effect against cholesterol accumulation, the major component of atherosclerosis (Colwell et al., 1981). The level of these lipoproteins decreases when other heart disease risk factors are present and increases in their absence. This indicates that high-density lipoproteins (HDL) can be used as a

reliable heart disease risk indicator (Francis, 1980).

In order to examine the relationship of diabetic control and heart disease risk, high-density lipoprotein levels can be correlated with glycosylated-hemoglobin levels (See Section K, Figure 1). Glycosylated hemoglobin provides a quantitative assessment of heart disease risk over several preceding weeks. This is an inverse relationship -- as glycosylated-hemoglobin levels decrease, high-density lipoprotein levels increase (Calvert, Mannik, Graham, Wise & Yeates, 1978).

This investigation used the continuous subcutaneous insulin infusion pump to improve diabetic control after a period of time (control period) in which the diabetic person used conventional insulin injections (See Section L, Figure 1). Glycosylated hemoglobin and high-density lipoprotein levels were recorded during the control period, just before instituting the infusion pump and after the infusion pump had been used for three months. These data were used to determine the effect of diabetic control on heart disease risk.

Purpose and Problem

The general purpose of this study was to describe the relationship between indicators of diabetic control and heart disease risk in diabetic subjects using conventional insulin injections and those same indicators when the diabetics were receiving continuous subcutaneous insulin infusion from a portable battery powered pump.

Research Questions

The research questions were:

1. Will Hb Alc and HDL levels change during a six month control period of conventional insulin management of diabetes?

2. Will Hb Alc and HDL levels be inversely related during a six month control period?

3. Will Hb Alc levels decrease from control period levels after the insulin pump has been used for three months?

4. Will HDL levels increase from control period levels after the insulin pump has been used for three months?

5. Will Hb Alc and HDL levels be inversely related after three months of insulin pump use?

6. Will an inverse relationship exist between HDL and cholesterol levels?

7. Will an inverse relationship exist between HDL and triglyceride levels?

Definitions

Diabetic Person: A diabetic person was a person who required exogenous insulin to maintain normoglycemia. Additionally, a diabetic person involved in this investigation had neuropathy and possibly nephropathy or retinopathy. An internist, opthamologist, and neurologist respectively documented these microvascular complications by medical history, physical examinations and laboratory tests.

Diabetic Control: Diabetic control was control of glucose

homeostasis which was achieved by the adequate administration of exogenous insulin. The measurement of long-term diabetic control was the blood Hb Alc level, and the measurement of current diabetic control was blood-glucose levels as measured by standard laboratory procedure.

Heart Disease Risk: Heart disease risk was the considered potential or risk a person had for the development of CAHD. The index of heart disease risk was the blood HDL levels as measured by standard laboratory procedure.

Control Period: The control period was a period of six continuous months in which the diabetic person continued to use conventional insulin injections to effect diabetic control.

Experimental Period: The experimental period was a period of three consecutive months in which the diabetic person used the continuous subcutaneous insulin infusion pump to effect diabetic control.

CHAPTER II

METHODOLOGY

Overview

This investigation used a descriptive research approach, with all subjects who met the study criteria acting as their own controls. After a control period using conventional insulin injections, insulin infusion pump treatment was instituted and used for the experimental period. This study described changes in Hb Alc and HDL levels during the control and experimental periods.

Sample

This study used a convenience sample of five diabetic subjects who were participating in a study conducted by four physicians. The criteria for these subjects was the presence of measurable peripheral neuropathy, and a willingness to complete study requirements. Other complications of diabetes may have been present. Any subjects excluded were those excluded from the larger study. Data obtained from these subjects was used to answer the research questions.

Procedure

This investigation took place simultaneously with a larger study by four physicians. The subjects continued with biweekly or

more frequent appointments with the physicians for assessment of diabetic control, laboratory procedures, and physican examination as scheduled. All laboratory tests were done at a hospital except the capillary blood glucose determinations which were done by the subjects at home.

Basal flow rate and bolus amounts of insulin, blood glucose levels before meals and at bedtime, and other events related to diabetic control were recorded by the subjects on data sheets designed for the larger study. The physician and subject reviewed the data sheet during each clinic appointment to assess diabetic control during the preceding two weeks.

This investigation involved a control and experimental period lasting six and three continuous months respectively. During the control period, the subjects continued using conventional insulin injections. Within the first and final week of the control period, Hb Alc and HDL levels were measured. In the first week of the experimental period, the subjects were instructed as outpatients in the operation and management of the continuous subcutaneous insulin infusion pump.

Determination of the insulin infusion pump basal flow and bolus rates were calculated from the insulin dose used in the control period. These calculated flow rates required further adjustment after diabetic control was assessed while the subject was using the infusion pump. Repeated changes in insulin flow rates were usually necessary before desired diabetic control was achieved.

The subjects used the infusion pump throughout the experimental

period. During the final week of the experimental period, Hb Alc and HDL levels were again measured. Relationships of Hb Alc and HDL levels were compared and described.

Instruments

Routine equipment which included tourniquet, needle, needle holder, and vacu-tainer, were used to collect blood samples for Hb Alc and HDL levels.

The hospital laboratory received the blood samples and quantified Hb Alc and HDL levels. The Hb Alc levels were determined by using the Fast Hemoglobin TM Test System (distributed by Isolab Incorporated). The HDL levels were determined by a Micro-Centrifical-Analyzer Multi-Stat III (manufactured by Instrumentation Lab).

The insulin infusion pump was an Auto-Syringe Model AS-6C. The overall size of the pump was 3.3 x 6.3 x 1.0 inches; the weight, 9.6 ounces. The pump could be programmed for basal flow rate and bolus amounts with an accuracy of flow rate of ± 1%.

A 3 cc. syringe was used to store the prescribed amount of regular insulin which had been diluted with normal saline to make a total volume of 2.8 cc. The dilution was determined individually for each subject in order to last a minimum of 24 hours.

A digital display showed "distance units" of insulin to be infused in 24 hours. Each distance unit equaled 0.028 cc. of diluted insulin. Since 100 distance units were in 2.8 cc. and the number of diluted insulin units were known, the number of insulin units in each distance unit could be calculated.

Alarms were programmed to sound when the battery was low, insulin infusion was too rapid (runaway), high pressure or an obstruction was present. Two rechargeable batteries were used, each of which lasted for 24 hours. The insulin pump was encased with a high impact plastic case which also covered the syringe.

Micro-Volume Extension Sets were connected to the syringe in the pump by a Luer-Lock Adapter. The 42 inch tubing was soft, pliable and kink resistant. A 27-gauge needle was connected to the tubing. The needle was inserted into the abdomen, and the tubing was secured to the skin using adhesive or plastic tape.

The infusion pump was carried on a belt inconspicuously at the subject's side. Both the infusion pump and tubing were contained in a carrying case which had a loop for the insertion of a belt. While the case was attached to the belt, one side could be detached for operating the pump and viewing the digital display. When the subjects were sleeping, the pump was placed under the pillow or on a bedside stand.

Subjects monitored their diabetic control at home by measuring blood-glucose using glucose oxidase reagent sticks (Dextrostix, Ames Company) before each meal and at bedtime. The results of each blood-glucose determination were recorded on data sheets by the subjects.

Human Subjects Considerations

Diabetic subjects signed an informed consent for this investigation. Since this investigation took place simultaneously with

the study by four physicians, extra blood samples were not needed for Hb Alc and HDL level determination. The subjects were under physician supervision throughout the investigation. All services and procedures related to the study were done without expense to the subjects. Also, subject identification was not revealed in reporting investigation results.

CHAPTER III

RESULTS

Group Biographical Data

Five subjects completed the study requirements, four female and one male. The age ranged from 26 years to 31 years with a mean age of 27.8 years.

Four of the five subjects (80%) had a family history of diabetes mellitus. Table 2 describes the incidence of diabetes for family members. Family history was separated into groups of siblings, parents, maternal ancestry line, and paternal ancestry line. Ancestry lines include aunts, uncles, cousins, and grandparents.

Table 3 presents the subjects' age of diabetic onset, years duration of diabetes, and years of insulin use. The age of onset ranged from 10 to 25 years with a mean of 14.6 years. The duration of diabetes ranged from 5 to 15 years with a mean of 12.4 years. The years of insulin use also ranged from 5 to 15 years with a mean of 12.4 years.

Prestudy insulin dose, type of insulin, and injection schedule are provided in Table 4. Total insulin dose ranged from 30 to 50 units. Four subjects used mixed insulins. Three subjects used insulin twice a day, one used insulin once a day and one used

Table 2

Incidence of Diabetes for Family Members

Subject	Siblings	Parents	Maternal Ancestry Line	Paternal Ancestry Line
1	--	1	--	1
2	--	--	--	2
3	1	--	--	--
4	--	--	--	--
5	2	--	--	--
Total	3	1	0	3

Table 3

Diabetes History

Subject	Age of Onset	Years Duration	Years of Insulin Use
1	10	15	15
2	10	15	15
3	16	13	13
4	25	5	5
5	12	14	14
Mean Value	14.6	12.4	12.4

Table 4

Prestudy Insulin Dose and Schedule

Subject	A.M.			Noon			P.M.		
	S[a]	I[b]	L[c]	S	I	L	S	I	L
1	15	15	--	--	--	--	10	5	--
2	10	12	--	--	--	--	6	8	--
3	5	--	--	5	--	--	8	18	--
4	--	20	10	--	--	--	--	10	10
5	--	30	--	--	--	--	--	--	--

[a]S = Short-acting insulin

[b]I = Intermediate-acting insulin

[c]L = Long-acting Insulin

Note. Dosages given in units of insulin.

insulin three times a day.

All subjects had one or more diabetic complication as documented by medical history, physical exam, and diagnostic tests. These complications included neuropathy, retinopathy, and renal disease. Table 5 shows the distribution of diabetic complications. Most prevalent complications included neuropathy (100%) and retinopathy (80%).

Indicators of Diabetic Control and Heart Disease Risk

The intent of this investigation was to describe the relationship of diabetic control and heart disease risk indicators of subjects while using conventional insulin injections and while using the continuous subcutaneous insulin infusion pump. The subjects were followed for a six-month control period in which they continued to use conventional insulin injections for diabetic control. During the first and last weeks of the control period, Hb Alc, HDL, cholesterol and triglyceride levels were obtained. The study period consisted of the next consecutive three months when the subjects used insulin infusion pumps to obtain diabetic control. During the last week of the study period, Hb Alc, HDL, cholesterol and triglyceride levels were again measured. In reporting laboratory data, this study used normal values as defined by the hospital that conducted the tests. These values were:

Hb Alc	5.5 - 8.5% hemoglobin (Hgb)
HDL	38-75 mg/dl

Table 5

Diabetic Complications

Subject	Neuropathy	Retinopathy	Renal Disease
1	+	+	+
2	+	+	-
3	+	+	-
4	+	+	+
5	+	-	-
Total	5	4	2

Cholesterol	140 - 275 mg/dl
Triglyceride	50 - 200 mg/dl

Findings for each subject and for the group as a whole are in the following sections.

Subject Number One

Subject one was a 26-year-old male with a diabetic father and paternal grandfather. This subject was 10 years of age at the onset of diabetes, has now had diabetes for 15 years, and has taken insulin for the entire time. Prestudy insulin dose and schedule were 15 units of regular insulin and 15 units of intermediate-acting insulin in the morning in addition to 10 units of regular and 5 units of intermediate-acting insulin in the evening. Existing diabetic complications included retinopathy, renal disease, and neuropathy. All laboratory results for subject one are reported in Table 6. Relationships between Hb Alc, HDL, cholesterol, and triglyceride levels are shown in Figure 2 for precontrol period, postcontrol period, and poststudy period results.

The Hb Alc level increased from 10.9% to 14.6% hemoglobin (Hgb) during the control period, then decreased to 9% hemoglobin (Hgb) at the end of the study period, which was 1.9% Hgb below precontrol period level. Levels of HDL decreased from 42 to 36 mg/dl during the control period and remained at 36 mg/dl during the study period. During the control period, the increase in Hb Alc and decrease in HDL created an inverse relationship. During the study period, the Hb Alc decreased while HDL remained at the same level.

Table 6

Laboratory Results for Subject One

Laboratory Test	Control Period		Study Period Insulin Pump Use
	0	6 months	9 months
HbAlc	10.9% Hgb	14.6% Hgb	9% Hgb
HDL	42 mg/dl	36 mg/dl	36 mg/dl
Cholesterol	202 mg/dl	239 mg/dl	261 mg/dl
Triglyceride	284 mg/dl	528 mg/dl	631 mg/dl

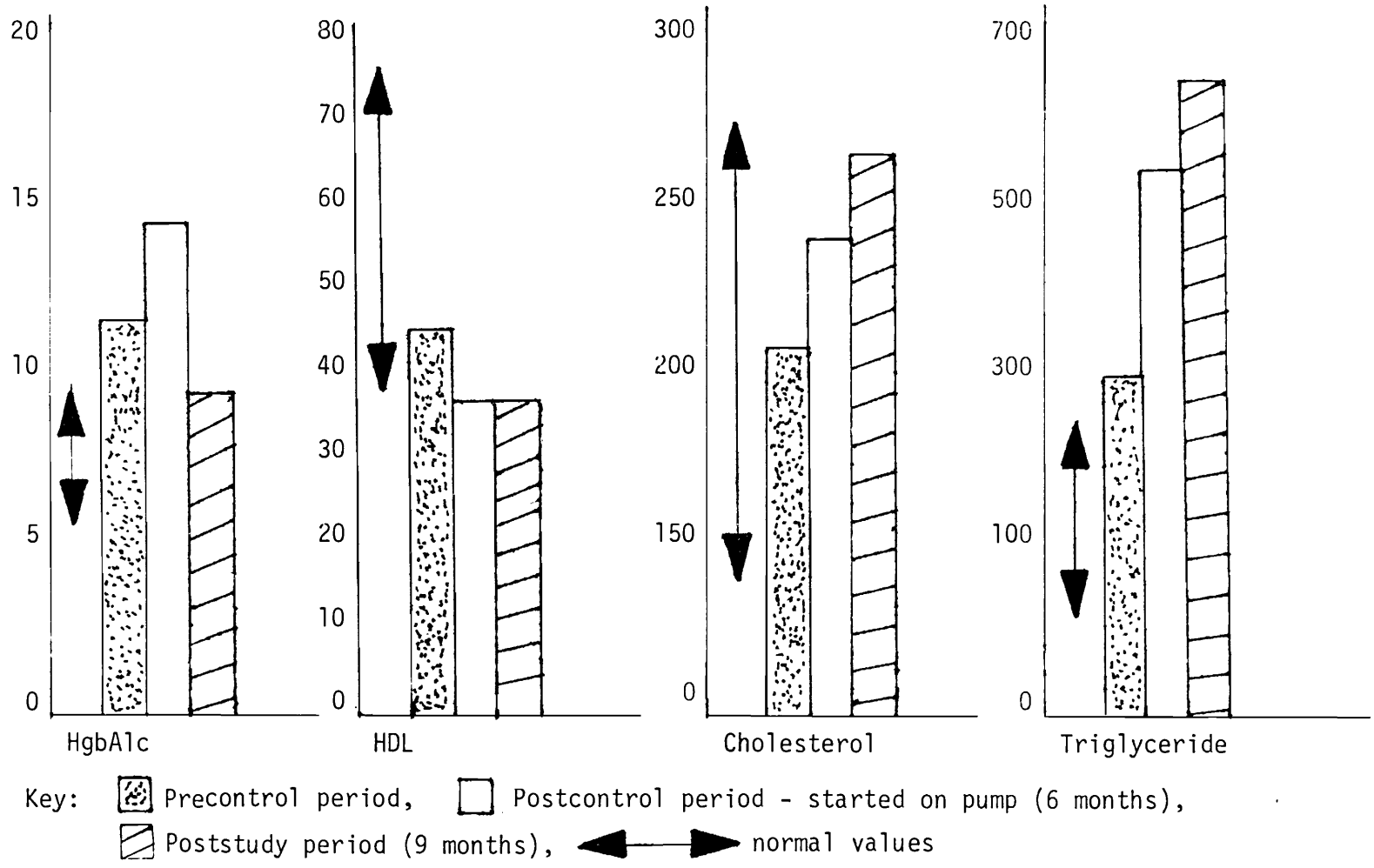

Figure 2. Subject One. Relationship of Laboratory Test Results.

Cholesterol levels increased from 202 to 239 mg/dl during the control period, then continued to increase from 239 to 261 during the study period. All cholesterol levels remained within normal limits. During the control period, the relationship between HDL and cholesterol was inverse due to the decrease in HDL and increase in cholesterol levels. During the study period, HDL remained at the same level as cholesterol continued to increase.

Triglyceride levels increased from 284 to 528 mg/dl during the control period, then continued to increase from 528 to 631 mg/dl during the study period. A triglyceride level of 631 mg/dl is three times the upper normal limit of 200 mg/dl. During the control period, an inverse relationship existed between HDL and triglyceride. During the study period, the HDL remained at the same level as the triglyceride level increased.

In summary, Hb Alc increased during the control period and then decreased during the study period. The HDL level decreased after the control period and remained at the same level. The Hb Alc and HDL had an inverse relationship during the control period. Levels of HDL were inversely related during the control period with both cholesterol and triglyceride, and as HDL remained at the same level, cholesterol and triglyceride continued to increase.

Subject Number Two

Subject two was a 26-year-old female with a diabetic paternal half-sister and a first cousin. This subject was 10 years old at the onset of diabetes, has now had diabetes for 15 years, and has taken

insulin for the entire time. Prestudy insulin dose included 10 units of regular and 12 units of intermediate acting insulin in the morning plus 6 units of regular and 8 units of intermediate-acting insulin in the evening. Diabetic complications consisted of neuropathy and retinopathy. All laboratory results for subject two are given in Table 7. Relationships between HbAlc, HDL, cholesterol, and triglyceride levels are depicted in Figure 3 for precontrol period, postcontrol period, and poststudy period results.

The HbAlc levels decreased from 20.1 to 17% Hgb during the control period and continued to decrease from 17 to 12.1% Hgb during the study period. Levels of HDL increased from 28 to 56 ml/dl during the control period, then decreased from 56 to 52 mg/dl during the study period. During the control period, an inverse relationship between HbAlc and HDL was produced by the decrease in HbAlc and increase in HDL. During the study period, a direct relationship between HbAlc and HDL was produced by a decrease in both levels.

Cholesterol levels decreased from 598 to 282 mg/dl during the control period which was 2.1 times less. Cholesterol then increased from 282 to 293 mg/dl during the study period. The relationship between HDL and cholesterol was inverse during the control period, as HDL increased and cholesterol decreased. During the study period, an inverse relationship also existed as HDL decreased and cholesterol increased.

Triglyceride levels increased from 832 to 1250 mg/dl during the control period, then decreased from 1250 to 168 mg/dl during the study period which was 13% as much as the peak value. The relationship between HDL and triglyceride was direct during the control

Table 7

Laboratory Results for Subject Two

Laboratory Test	Control Period		Study Period Insulin Pump Use
	0	6 Months	9 Months
Hb A1c	20.1% Hgb	17.0% Hgb	12.1% Hgb
HDL	28 mg/dl	56 mg/dl	52 mg/dl
Cholesterol	598 mg/dl	282 mg/dl	293 mg/dl
Triglyceride	832 mg/dl	1250 mg/dl	168 mg/dl

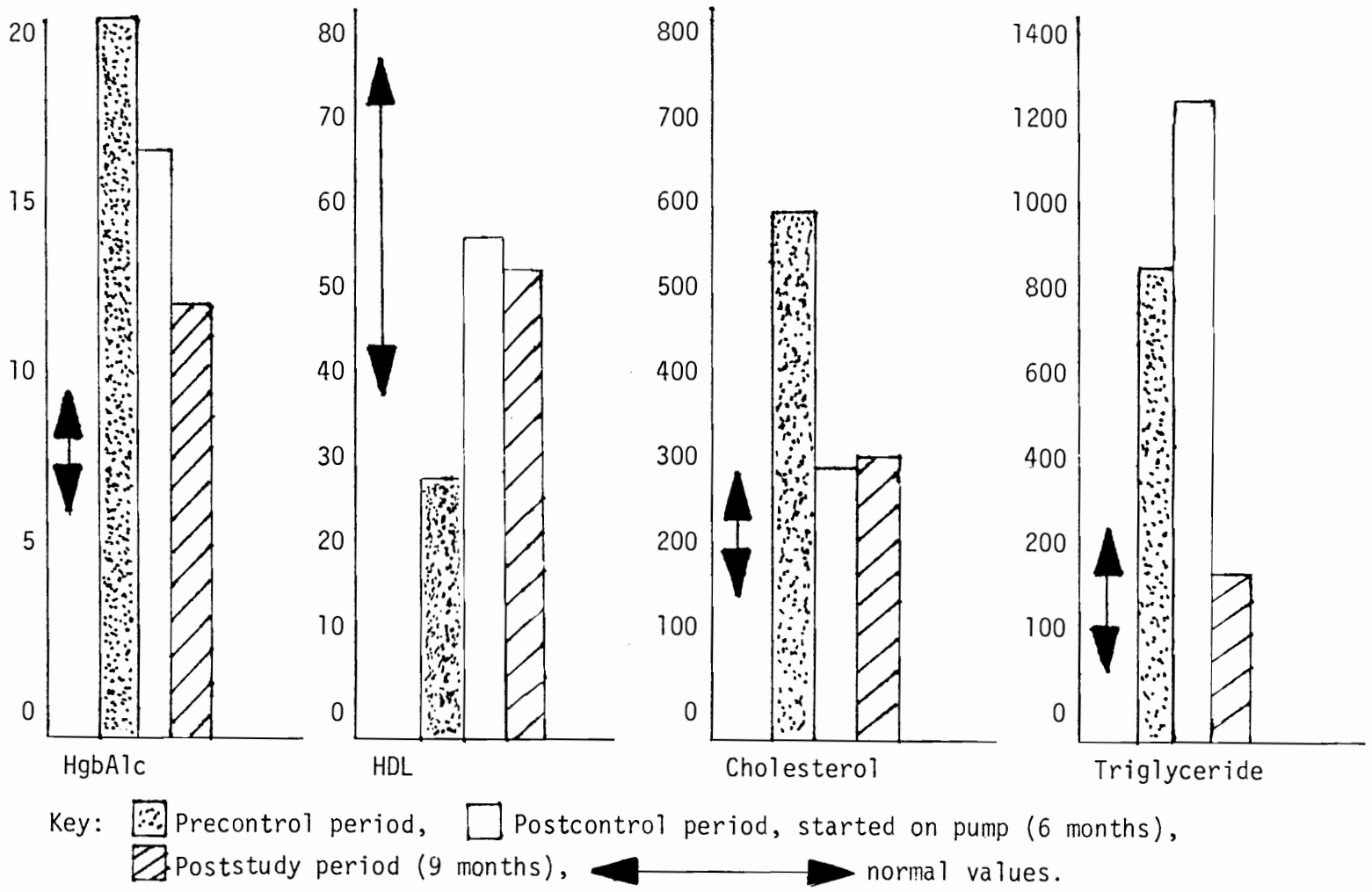

Figure 3. Subject Two. Relationship of Laboratory Test Results.

period as both levels increased. During the study period, the relationship between HDL and triglyceride was also direct as both levels decreased.

In summary, there was an inverse relationship between Hb Alc and HDL levels during the control period and a direct relationship during the study period. Levels of HDL and cholesterol had an inverse relationship during both the control and study periods, while HDL and triglyceride levels had a direct relationship.

Subject Number Three

Subject three was a 30-year-old female with a diabetic sister. This subject was 16 years old at the onset of diabetes, has now had diabetes for 13 years, and has taken insulin for the entire time. Prestudy insulin dose consisted of 5 units of regular insulin in the morning and at noon, with 8 units of regular and 18 units of intermediate-acting insulin in the evening. Diabetic complications included retinopathy, cataracts, and neuropathy. All laboratory results are given in Table 8. The relationship between Hb Alc, HDL, cholesterol, and triglyceride levels is given in Figure 4 for precontrol period, postcontrol period and poststudy period results.

Levels of Hb Alc decreased from 11 to 9.1% Hgb during the control period, then increased from 9.1 to 10.3% Hgb during the study period. The HDL levels decreased from 54 to 50 mg/dl during the control period, then increased from 50 to 53 mg/dl during the study period. The relationship between Hb Alc and HDL was direct during both control and study periods. As Hb Alc decreased, HDL decreased, then when Hb Alc increased, HDL increased.

Table 8

Laboratory Results for Subject Three

Laboratory Test	Control Period		Study Period Insulin Pump Use
	0	6 Months	9 Months
HbA1c	11% Hgb	9.1% Hgb	10.3% Hgb
HDL	54 mg/dl	50 mg/dl	53 mg/dl
Cholesterol	186 mg/dl	175 mg/dl	198 mg/dl
Triglyceride	135 mg/dl	162 mg/dl	84 mg/dl

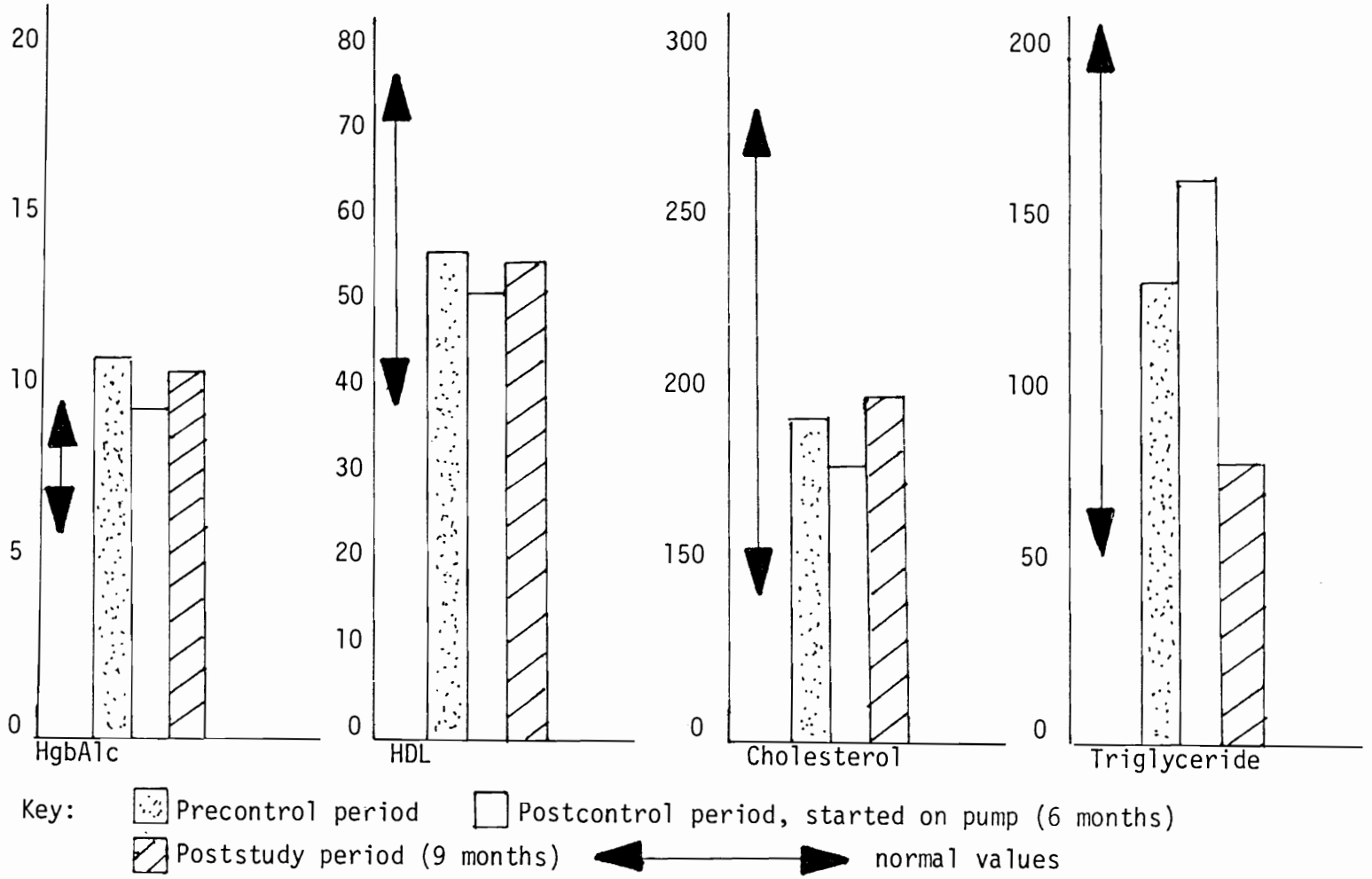

Figure 4. Subject Three. Relationship of Laboratory Results.

Cholesterol levels decreased from 186 to 175 mg/dl during the control period, then increased from 175 to 198 mg/dl during the study period. The relationship between HDL and cholesterol was direct during both control and study periods. As HDL decreased, cholesterol decreased; and when HDL increased, cholesterol increased.

Triglyceride levels increased from 135 to 162 mg/dl during the control period, then decreased from 162 to 84 during the study period. The relationship between HDL and triglyceride was inverse during both the control and study period. As HDL decreased, triglyceride increased, and then as HDL increased, triglyceride decreased.

In summary, all levels remained within normal limits, except Hb Alc. There existed a direct relationship between Hb Alc and HDL throughout the control and study periods. The HDL relationship with cholesterol was direct, in contrast to an inverse relationship with triglyceride.

Subject Number Four

Subject four was a 31-year-old female who had no family history of diabetes. This subject was 25 years old at the onset of diabetes, has now had diabetes for 5 years, and has taken insulin for the entire time. Prestudy insulin dose was 20 units of intermediate-acting insulin and 10 units of long-acting insulin in the morning, plus 10 units of intermediate-acting insulin and 10 units of long-acting insulin in the evening. Diabetic complications included retinopathy and neuropathy. All laboratory test results are reported in Table 9. Relationships between Hb Alc, HDL, cholesterol and triglyceride are

Table 9

Laboratory Results for Subject Four

Laboratory Test	Control Period		Study Period Infusion Pump Use
	0	6 Months	9 Months
HbA1c	17.3% Hgb	19.2% Hgb	11.7% Hgb
HDL	60 mg/dl	80 mg/dl	62 mg/dl
Cholesterol	160 mg/dl	211 mg/dl	138 mg/dl
Triglyceride	176 mg/dl	132 mg/dl	133 mg/dl

shown in Figure 5 for precontrol period, postcontrol period, and poststudy period results.

Levels of HbAlc increased from 17.3 to 19.2 Hbg during the control period, then decreased from 19.2 to 11.7 during the study period. The HDL levels increased from 60 to 80 mg/dl during the control period, then decreased from 80 to 62 mg/dl during the study period. Precontrol period and poststudy levels of HDL had a difference of 2 mg/dl. The relationship between HbAlc and HDL was direct during both the control and study periods. As HbAlc increased, HDL increased; and as HbAlc decreased HDL decreased.

Cholesterol levels increased from 160 to 211 mg/dl during the control period, then decreased from 211 to 138 mg/dl during the study period. The relationship between HDL and cholesterol was direct during both the control and study periods. As HDL increased, cholesterol increased; and as HDL decreased, cholesterol decreased.

Triglyceride levels decreased from 176 to 132 mg/dl during the control period, then increased from 132 to 133 during the study period. The relationship between HDL and cholesterol was inverse during both the control and study periods. As HDL increased triglyceride decreased; and as HDL decreased, triglyceride increased, although the increase in triglyceride during the study period was only 1 mg/dl. Cholesterol and triglyceride levels were clinically within normal limits with a difference no greater than 2.

In summary, a direct relationship existed between HbAlc and HDL. The relationship between HDL and cholesterol was direct, in contrast to the inverse relationship between HDL and triglyceride.

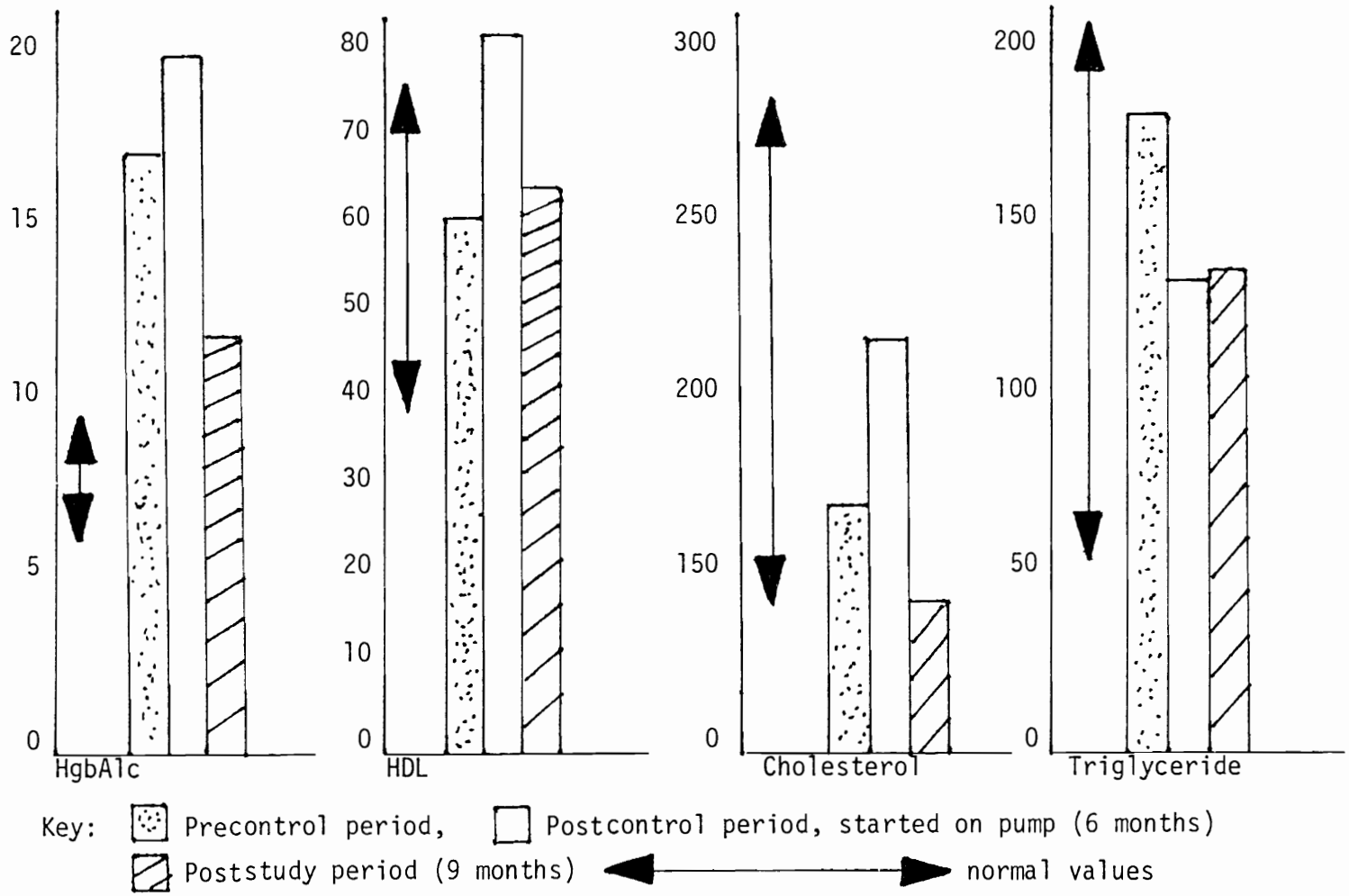

Figure 5. Subject Four. Relationship of Laboratory Results.

Subject Number Five

Subject five was a 26-year-old female with a diabetic brother and sister. This subject was 12 years old at the onset of diabetes and has had diabetes for 13½ years, and has taken insulin for 13 years. Prestudy insulin dose was 30 units of intermediate-acting insulin taken in the morning. Diabetic complications consisted of neuropathy and retinopathy. All laboratory test results are given in Table 10. Relationships between Hb Alc, HDL, cholesterol, and triglyceride levels are described in Figure 6 for precontrol period, postcontrol period, and poststudy period results.

The Hb Alc levels decreased from 16.9 to 16.7% Hgb during the control period, and continued to decrease from 16.7% to 12.3% Hgb during the study period. Levels of HDL decreased from 91 to 69 mg/dl during the control period, and continued to decrease from 69 to 66 mg/dl during the study period. The relationship between Hb Alc and HDL was direct during both the control and study periods. As Hb Alc decreased, HDL decreased.

Cholesterol levels increased from 166 to 179 mg/dl during the control period, then decreased from 179 to 152 mg/dl during the study period. All cholesterol levels were within normal limits. The relationship between HDL and cholesterol was inverse during the control period which was produced by a decrease in HDL and increase in cholesterol. During the study period, a direct relationship existed between HDL and cholesterol which was produced by a decrease in both HDL and cholesterol.

Triglyceride levels decreased from 75 to 72 mg/dl during the

Table 10

Laboratory Results for Subject Five

Laboratory Test	Control Period		Study Period Infusion Pump Use
	0	6 Months	9 Months
Hb A1c	16.9% Hgb	16.7% Hgb	12.3 % Hgb
HDL	91 mg/dl	69 mg/dl	66 mg/dl
Cholesterol	166 mg/dl	179 mg/dl	152 mg/dl
Triglyceride	75 mg/dl	72 mg/dl	37 mg/dl

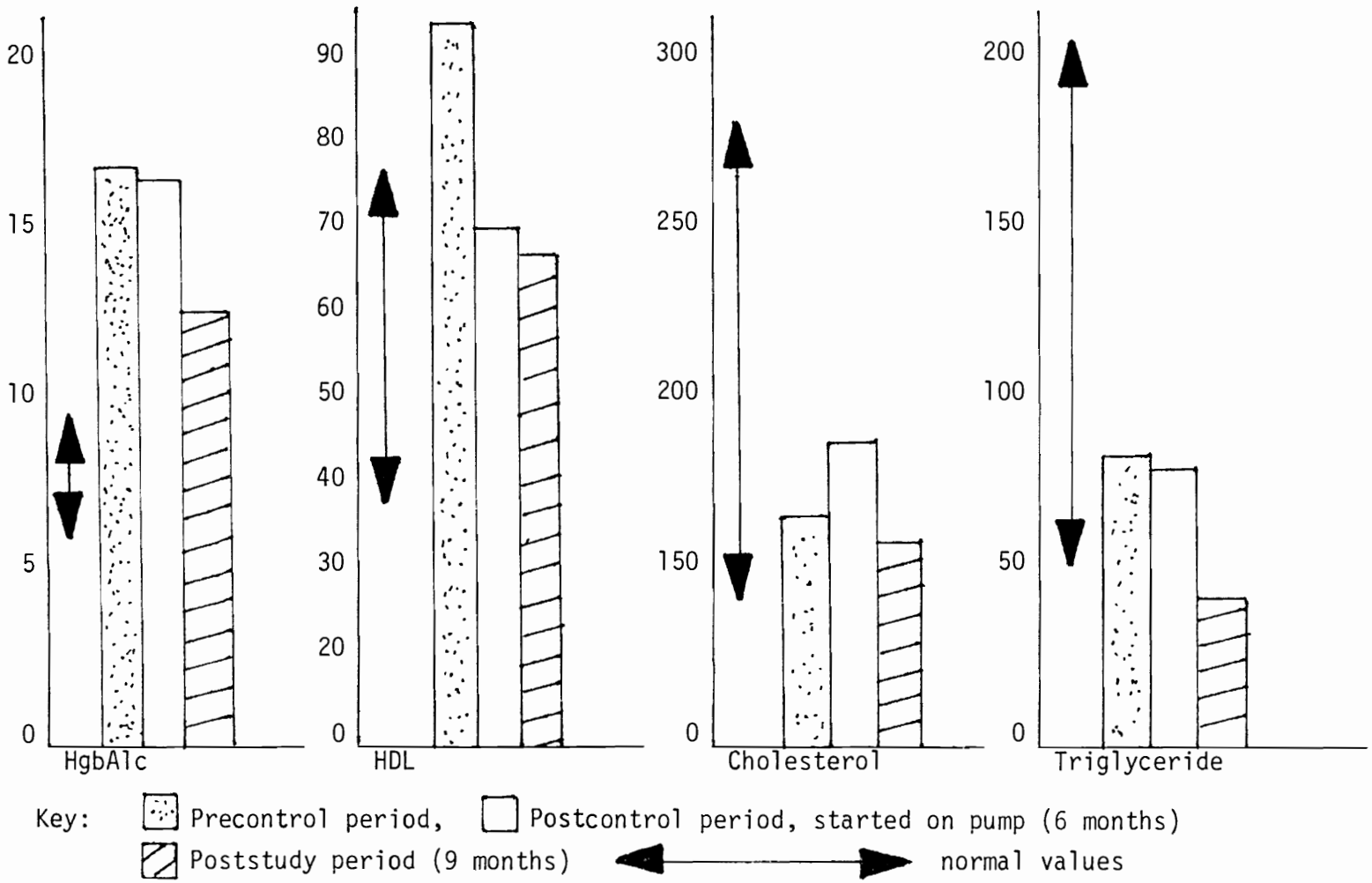

Figure 6. Subject Five. Relationship of Laboratory Results.

control period and continued to decrease from 72 to 37 mg/dl during the study period. The relationship between HDL and triglyceride was direct during both control and study periods. As HDL levels decreased, triglyceride levels decreased.

In summary, there was a direct relationship between Hb Alc and HDL during the control and study periods, although there was an insignificant change in Hb Alc during the control period, and an insignificant change in HDL during the study period. The relationship between HDL and cholesterol was inverse during the control period and was direct during the study period. The relationship between HDL and triglyceride was direct for both control and study periods.

The Group As A Whole

The range and mean values of Hb Alc, HDL, cholesterol, and triglyceride for the precontrol period, postcontrol period, and poststudy period are given in Table 11. The relationships between Hb Alc, HDL, cholesterol and triglyceride mean levels are depicted in Figure 7.

The mean Hb Alc increased from 15.24 to 15.32% Hgb during the control period, then decreased from 15.32 to 11.08% Hgb during the study period. Levels of mean HDL increased from 55 to 58.2 mg/dl during the control period, then decreased from 58.2 to 53.8 mg/dl during the study period. All mean HDL levels were within normal range. The relationship between mean Hb Alc and HDL was direct for both the control and study periods. As Hb Alc increased, HDL increased; as Hb Alc decreased, HDL decreased.

Table 11

Laboratory Results for the Group as a Whole

Laboratory Test	Control Period				Study Period Insulin Pump Use	
	0 months		6 months		9 months	
	Range	Mean	Range	Mean	Range	Mean
HbA1c	10.9-20.1 % Hgb	15.24% Hgb	9.1-19.2 % Hgb	15.32% Hgb	9-12.3% Hgb	11.08% Hgb
HDL	28-91 mg/dl	55 mg/dl	36-80 mg/dl	58.2 mg/dl	36-66 mg/dl	53.8 mg/dl
Cholesterol	160-598 mg/dl	262.4 mg/dl	175-282 mg/dl	217.2 mg/dl	138-293 mg/dl	208.4 mg/dl
Triglyceride	78-832 mg/dl	300.4 mg/dl	72-1250 mg/dl	428.8 mg/dl	37-631 mg/dl	210.6 mg/dl

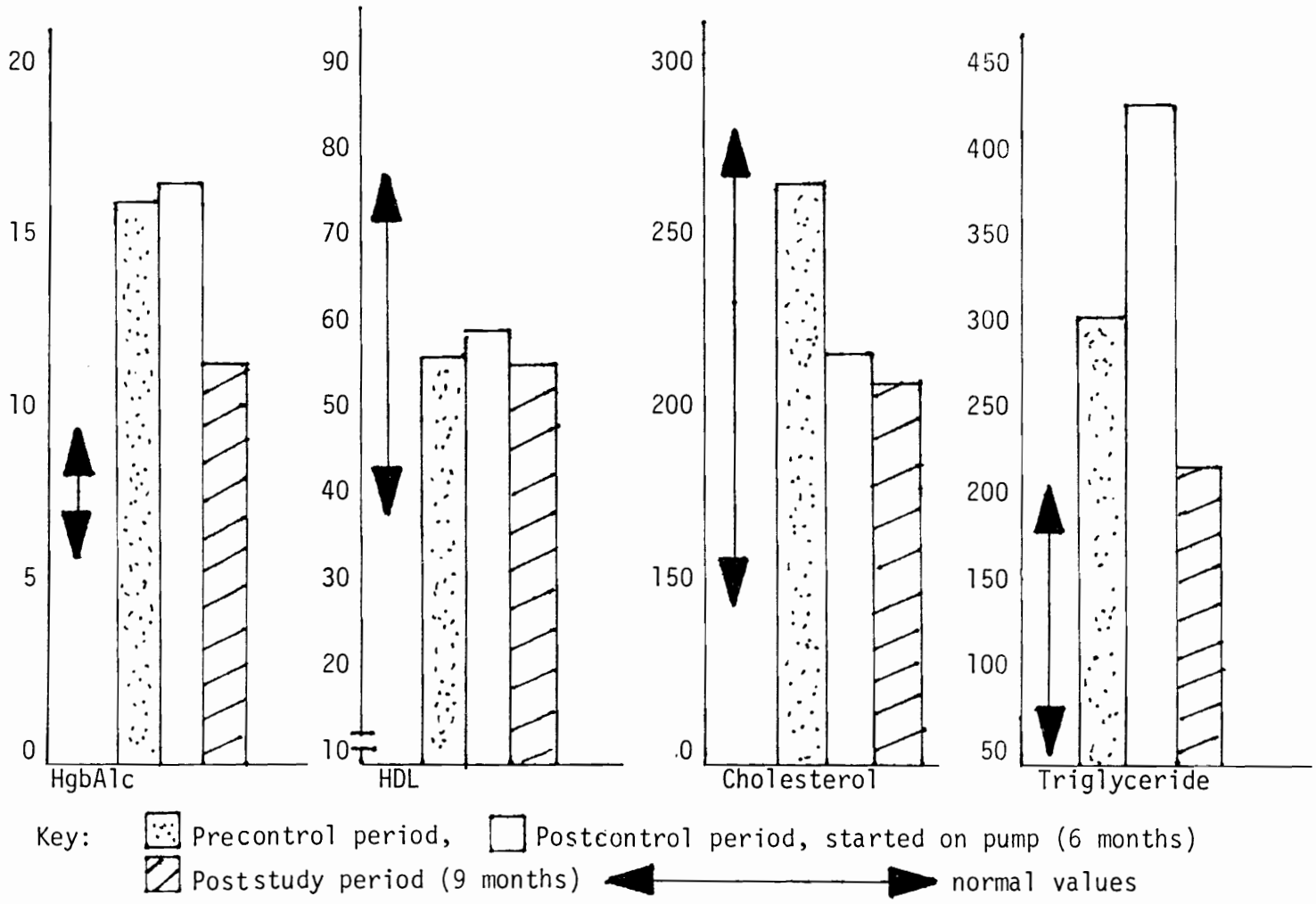

Figure 7. Group as a Whole. Relationship of Mean Laboratory Results.

Mean cholesterol levels decreased from 262.4 to 217.2 mg/dl during the control period, and continued to decrease from 217.2 to 208.4 mg/dl during the study period. The relationship between mean HDL and cholesterol was inverse during the control period, then direct during the study period. As HDL increased, cholesterol decreased, and as HDL decreased, cholesterol decreased.

Mean triglyceride levels increased from 300.4 to 428.8 mg/dl during the control period, then decreased from 428.8 to 210.6 mg/dl during the study period. The relationship between mean HDL and triglyceride was direct. As HDL increased, triglyceride increased; as HDL decreased, triglyceride decreased.

In summary, mean Hb Alc and HDL had a direct relationship during the control and study periods. The mean HDL had an inverse relationship with cholesterol during the control period then a direct relationship during the study period. Whereas mean HDL and triglyceride had a direct relationship during both the control and study periods.

This chapter has described the five diabetic subjects as individuals and as a group. Laboratory results and relationships of Hb Alc, HDL, cholesterol, and triglyceride have been given in tables and figures for precontrol, postcontrol, and poststudy periods.

CHAPTER IV

DISCUSSION, SUMMARY, AND RECOMMENDATIONS

Discussion

The leading cause of death in the industrialized world is CAHD. In the general population, the morbidity of CAHD is significantly greater for diabetic persons in comparison to nondiabetic persons. Current data give evidence that the atherosclerotic process in diabetic persons does not differ from nondiabetic persons. However, the atherosclerotic process proceeds more rapidly and extensively in diabetic persons. Researchers believe that the inherent characteristics of the diabetic state contribute to the acceleration and extensiveness of atherosclerosis observed in diabetic persons. Diabetic control -- normoglycemia and normal insulinemia -- can decrease these inherent diabetic characteristics which are directly related to atherosclerosis. Therefore, diabetic control may decrease and possibly slow the progression of atherosclerosis in diabetic persons. Better diabetic control can be provided by the continuous subcutaneous insulin infusion pump than by conventional insulin injections, according to the literature.

Indicators for long-term diabetic control and heart disease risk are Hb Alc and HDL respectively. These indicators have been

employed to determine the relationship of diabetic control and heart disease risk while the diabetic subject was using conventional insulin injections and while the subject was using the continuous subcutaneous insulin infusion pump. The purpose of this study was to describe the effect of diabetic control on heart disease risk.

Group Biographical Data

The mean age for the five subjects was 27.8 years with a mean of 12.4 years duration of diabetes. An identical average age group of nondiabetic persons would not be expected to have the chronic health problems seen in this young age sample. One hundred percent of this sample of diabetic subjects have developed one or more diabetic complications within the last 5 to 15 years. These diabetic complications -- neuropathy, retinopathy, and renal disease -- are directly associated with inadequate or poor diabetic control.

At the end of this investigation, some changes in renal function tests were documented, while changes in retinopathy and neuropathy will be documented later. For the two subjects with renal disease (subjects one and four), the disease increased during the control period but showed no change (subject one) or slight improvement (subject four) during the study period. This can be interpreted that as diabetic control improved, further decrease in renal function was halted.

Although no signs or symptoms of heart disease were found in this group of subjects, their medical history suggests heart disease is likely to develop in the future.

Indicators for Diabetic Control and Heart Disease Risk

Discussion of the relationship of indicators for diabetic control and heart disease risk will be given for each subject and then for the group as a whole. The research questions will be answered and discussed with conclusions.

For interpretation purposes, the following changes in Hb Alc, HDL, cholesterol, and triglyceride are considered insignificant:

Hb Alc	$\leq$ 2% Hgb
HDL	$\leq$ 5 mg/dl
Cholesterol	$\leq$ 9 mg/dl
Triglyceride	$\leq$ 9 mg/dl

Subject Number One. The Hb Alc increased during the control period but then decreased during the study period. This suggests that diabetic control was inadequate while the subject was using the conventional insulin injections. The use of the insulin pump provided improved control as demonstrated by the Hb Alc which decreased to clinically normal range (difference of 0.5% Hgb). This corresponds with the literature.

The HDL levels decreased during the control period and remained at the same level during the study period. The decrease in HDL and increase in Hb Alc, or inverse relationship, during the control period is consistent with the literature. The decrease in Hb Alc with the same level of HDL during the study period could be the result of diabetic control not being adequate enough for HDL levels to change. With continued use of the insulin pump and improved control, the

Hb Alc should continue to decrease and HDL should begin to increase.

The inverse relationship of HDL to cholesterol and triglyceride correlates with the literature. The increase in triglyceride with an increase of Hb Alc during the control period is also consistent with the literature, suggesting that poor diabetic control, with inadequate amounts of insulin, contributes to hypertriglyceridemia. The continued increase of triglyceride in the study period indicates that although diabetic control improved with the insulin pump, the control was not as good as it could have been.

In summary, this subject's diabetic control was better with the insulin pump than with insulin injections, showing clinically significant changes in Hb Alc during the control and study periods (3.7% Hgb increase and 5.6% Hgb decrease). An inverse relationship existed between Hb Alc and HDL during the control period, but as Hb Alc decreased during the study period, HDL remained the same. With these changes in HDL, both cholesterol and triglyceride levels increased, further suggesting diabetic control could have been better.

Subject Number Two. The Hb Alc decreased significantly throughout the control (3.1% Hgb) and study (4.9% Hgb) periods, although never reaching normal limits. This indicates diabetic control improved during both the control and study periods, with the best diabetic control obtained while the infusion pump was used. There was an inverse relationship between Hb Alc and HDL during the control period. The direct relationship in the study period can be clinically interpreted as an inverse relationship since the decrease

in Hb Alc level was significant (4.9% Hgb), whereas the decrease in HDL level was not clinically significant (4 mg/dl). These results are compatible with the literature.

An inverse relationship existed between HDL and cholesterol; which is congruent with literature reports. The significant increase in HDL (28 mg/dl) with a significant decrease in cholesterol (316 mg/dl) gives evidence to the significant improvement in diabetic control. A direct relationship existed between HDL and triglyceride which is not uniform with the literature. The high levels of triglyceride during the control period are a result of poor diabetic control as indicated by high Hb Alc levels. The significant decrease in triglyceride (1082 mg/dl) in the study period was a result of improved diabetic control. The relationship between HDL and triglyceride was a consequence of poor diabetic control, thus changing the HDL correlation.

In summary, this subject's diabetic control significantly improved during the control and study periods with the best control achieved with the insulin pump. A significant increase of HDL occurred in the control period with an insignificant decrease in the study period. There was an inverse relationship between Hb Alc and HDL during the control period and an insignificant direct relationship during the study period.

The relationship of HDL to cholesterol was inverse during the control and study periods with insignificant changes of both indicators in the study period. The relationship between HDL and triglyceride was direct, which was primarily due to inadequate

control during the control period as reflected by high Hb Alc levels. The significant decrease in triglyceride with insignificant decrease in HDL is meaningful and suggests an inverse clinical relationship.

Subject Number Three. The Hb Alc decreased during the control period (1.9% Hgb) but then increased during the study period (1.2% Hgb), although these changes are not clinically significant. This indicates that diabetic control was similar whether the subject was using insulin injections or the infusion pump. However, diabetic control could be more adequate with the use of the insulin pump. With continued adjustment in basal and bolus insulin amounts of the infusion pump, improved diabetic control should result when the proper insulin dosage schedule is achieved.

The HDL levels remained within normal limits with a decrease during the control period (4 mg/dl) and an increase during the study period (3 mg/dl). These changes are not clinically significant. A direct relationship existed between Hb Alc and HDL. This is not a significant finding, since changes in both Hb Alc and HDL are not clinically significant.

Cholesterol decreased during the control period but then increased during the study period with all changes being within normal limits. The direct relationship of cholesterol with HDL does not correspond with the literature. Therefore, the changes in cholesterol could be a result of dietary or other interference with the test results.

An inverse relationship existed between HDL and triglyceride; this is uniform with the literature. All triglyceride levels were

within normal limits. The significant decrease during the study period (78 mg/dl) is also an indicator of improved diabetic control.

In summary, diabetic control did not improve significantly while the subject was using the insulin pump, resulting in insignificant changes in Hb Alc and HDL. Cholesterol and triglyceride remained within normal limits, although significant changes occurred during the study period.

Subject Number Four. There was an increase in Hb Alc during the control period (1.9% Hgb) with a significant decrease during the study period (7.5% Hgb). This indicates better diabetic control was achieved with the infusion pump. Levels of HDL increased during the study period but then decreased to near precontrol period level, making a direct relationship with Hb Alc. This relationship does not correlate with the literature. However, as diabetic control improved, HDL levels remained within upper normal limits.

A direct relationship existed between HDL and cholesterol; this does not correlate with the literature. However, cholesterol remained within normal limits. Thus other factors such as dietary interference are contributing to the cholesterol level changes. The inverse relationship of HDL to triglyceride does correlate with the literature, although the change in triglyceride level is insignificant during the study period (1 mg/dl).

In summary, the relationships between Hb Alc and HDL, and HDL and cholesterol do not correlate with the literature. However, improved diabetic control is indicated by the significant decrease in Hb Alc during the study period while the infusion pump was being

used, and perhaps with more time diabetic control will be sufficient for HDL to increase and cholesterol to decrease. The relationship between HDL and triglyceride was inverse.

Subject Number Five. The insignificant decrease in Hb Alc levels (0.2% Hgb) during the control period indicated that diabetic control remained the same while using insulin injections. The significant decrease in Hb Alc (4.4% Hgb) during the study period indicated improved diabetic control while using the insulin infusion pump. The direct relationship of Hb Alc to HDL is not consistent with the literature. However, the insignificant decrease in HDL (3 mg/dl) during the study period with a significant decrease in Hb Alc (4.4% Hgb) suggested an inverse relationship may be forthcoming.

The relationship between HDL and cholesterol was inverse during the control period and direct during the study period. The insignificant decrease in HDL (3 mg/dl) during the study period with a significant decrease in cholesterol (27 mg/dl) suggest an inverse relationship. With this interpretation, the relationship between HDL and cholesterol was consistent with the literature.

The HDL and triglyceride relationship was direct. The insignificant decrease in triglyceride (3 mg/dl) with a significant decrease in HDL (22 mg/dl) during the control period, plus the significant decrease in the triglyceride (35 mg/dl) in the study period with an insignificant decrease in HDL (3 mg/dl) suggest an inverse relationship which was consistent with the literature. In addition, triglyceride and Hb Alc relationship was direct which was also

consistent with the literature and indicative of inadequate control.

In summary, improved diabetic control did occur when the insulin pump was used. Absolute relationships between HbAlc and HDL, HDL and cholesterol, and HDL and triglyceride levels were not consistent with the literature.

The Group as a Whole. An insignificant increase occurred in the group mean Hb Alc (0.08% Hgb) during the control period with a significant decrease (4.24% Hgb) during the study period. This indicated better diabetic control was achieved for the subjects when the infusion pump was used, which conformed to the literature. Levels of mean HDL increased (3.2 mg/dl) during the control period then decreased (4.4 mg/dl) during the study period which created a direct relationship between mean HDL and Hb Alc. This relationship does not correspond with the literature. However, the changes in HDL levels were insignificant when compared to Hb Alc levels during the study period.

The relationship between mean HDL and cholesterol was inverse during the control period and direct during the study period. Changes in HDL (4.4 mg/dl) and cholesterol (8.8 mg/dl) during the study period were insignificant clinically. A direct relationship existed between mean HDL and triglyceride during both the control and study periods. The significant changes in triglyceride levels (127.6 and 217.4 mg/dl) can be attributed to subject two whose triglyceride levels were 832 and 1250 mg/dl during the control period, which increased the mean value.

The direct relationship between mean Hb Alc and triglyceride

suggested that triglyceride values were also a function of Hb Alc levels, which was indicated by the significant drop in both Hb Alc and triglyceride during the study period. This correlated with the literature.

In summary, the group's diabetic control improved significantly while using the insulin infusion pump. The direct relationship between mean Hb Alc and HDL did not correspond with the literature. The relationship between mean HDL and cholesterol was inverse during the control period and was direct during the study period. A direct relationship existed between mean HDL and triglyceride.

Conclusion

The Hb Alc levels indicated that diabetic control improved during the control period, in three subjects (0.2 - 3.1% Hgb increase), which was likely to be an effect of participation in a diabetic control study. Diabetic control deteriorated for two subjects (1.9 - 3.7% Hgb decrease) during the control period which indicated insulin injections did not adequately control their diabetes. The mean Hb Alc levels indicated a 0.08% Hgb increase in Hb Alc which was an insignificant change in diabetic control during the control period. Therefore, Hb Alc levels did not change significantly during the six month control period for this group of subjects, although significant changes did occur in subjects one and two.

During the control period, HDL levels decreased in three subjects (4 - 22 mg/dl decrease) and increased in two subjects (20 - 28 mg/dl). An increase in HDL was expected in the three subjects

whose Hb Alc level decreased and diabetic control improved. A decrease in HDL was expected in the two subjects whose Hb Alc level increased and diabetic control deteriorated. The mean HDL level increased (3.2 mg/dl) during the control period. Therefore, HDL levels changed significantly during the six month control period in subjects two, four and five, but did not change significantly for the group as a whole.

Subjects one and two had an inverse relationship between Hb Alc and HDL during the control period. The direct relationship between Hb Alc and HDL in the other three subjects was not expected and did not conform with the literature. The mean Hb Alc and HDL levels for the group had a direct relationship with an insignificant increase in Hb Alc and a significant increase in HDL. Therefore, the relationship between Hb Alc and HDL was inverse for two subjects, although a direct relationship existed between Hb Alc and HDL for the group during the control period.

During the study period four subjects had a decrease in Hb Alc (4.4 to 7.5 % Hgb) and one subject had an increase in Hb Alc (1.2 % Hgb). The increase in Hb Alc (1.2% Hgb) in subject three was insignificant while using the insulin pump. Diabetic control improved in four subjects when using the insulin pump. The mean values for Hb Alc decreased during the study period which indicated diabetic control improved for the group when using the insulin pump. Therefore, Hb Alc levels decreased from control period levels after the insulin pump had been used for three months.

Although diabetic control improved for subjects during the

control and study periods, Hb Alc levels never decreased to normal values. Diabetic control could have been appreciably better with more aggressive management. This suggests that diabetic control can continue to improve with adjustments in the infusion pump basal and bolus rates.

During the study period HDL levels decreased in subject two, four, and five (3 - 18 mg/dl), remained the same for subject one, and increased in subject three (3 mg/dl). The increase of HDL in subject three was expected with improved diabetic control. The subjects whose HDL remained the same or whose HDL decreased did not conform to the expectation from the literature. Other influences on HDL levels are the risk factors for heart disease which this study did not control, such as diet and smoking. The mean HDL levels decreased (4.4 mg/dl) during the study period, which is not significant. Therefore, the HDL level did not increase from control levels after the insulin pump had been used for three months.

Subjects two, three, four, and five had a direct relationship between Hb Alc and HDL during the study period. The Hb Alc decreased as HDL remained at the same level in subject one. The mean values of Hb Alc and HDL also had a direct relationship. The lack of inverse relationship between Hb Alc and HDL is unexpected and does not correlate with the literature. Explanations for this are: a) Hb Alc did not decrease sufficiently to cause an inverse relationship; or b) other factors changed the Hb Alc and HDL values. Therefore, HbAlc and HDL levels were not inversely related after three months of insulin pump use.

An inverse relationship between HDL and cholesterol existed in subjects one, two and five during the control period, and existed in subject two during the study period. Although the number of subjects with this inverse relationship was lower than expected, subjects one, three, four, and five had all cholesterol levels within normal limits. The relationship of the mean values of HDL and cholesterol were inverse during the control period, then direct during the study period. This suggested that other uncontrolled variables must be influencing the HDL and cholesterol relationship. These variables may be heart disease risk factors such as diet and smoking. However, with the same or improved diabetic control, cholesterol levels decreased during both control and study periods, which suggested a relationship between Hb Alc and cholesterol. Therefore, the relationship between HDL and cholesterol was inverse only in the control period.

An inverse relationship between HDL and triglyceride existed in subjects one, three, and four during the control period, and existed in subject three during the study period. Three subjects had triglyceride levels within clinically normal range. The relationship between mean HDL and cholesterol was direct during both the control and study periods. This was not consistent with the literature. However, a direct relationship bewteen Hb Alc and triglyceride is consistent with the literature, indicating poor diabetic control or increased Hb Alc level is related to hypertriglyceridemia. Therefore, with increased Hb Alc levels, an inverse relationship could not exist between HDL and triglyceride.

Summary and Implications

The data in this study of diabetic subjects gives evidence that diabetic control can be significantly improved when using the continuous subcutaneous insulin infusion pump. Levels of Hb Alc did not change significantly during the six month control period when insulin injections were used. The Hb Alc decreased below control period levels after the infusion pump had been used for three months. However, the relationship between diabetic control (Hb Alc) and heart disease risk (HDL) could not be determined.

Levels of HDL did not change significantly during the control or study periods in this group of diabetic subjects. The relationship between Hb Alc and HDL was direct for both the control and study period. Relationships between HDL and cholesterol were inverse during the control period, then direct during the study periods. Relationships between HDL and triglyceride were direct for both the control and study periods. These results do not conform to the literature and suggest other variables are influencing these relationships. These variables are likely to be other heart disease risk factors. In addition, poor diabetic control produces increased triglyceride levels.

When determining the effect of diabetic control on heart disease risk, other variables in addition to diabetic control (Hb Alc) and heart disease risk (HDL) should be measured and controlled. These variables should include risk factors for heart disease which are age, family history, elevated lipid levels, diet, hypertension, smoking, lifestyle, and psychosocial tension.

Diabetic persons should be educated about the availability and use of the insulin infusion pump. These persons should be aware that diabetic control can improve significantly as indicated by this and other studies. When diabetic control is improved, a decrease in the rate and amount of diabetic complications should be seen. This is currently being studied in the larger investigation by four physicians.

Limitations and Recommendations

It was assumed in this study that the infusion pumps would function properly; the subjects could operate the infusion pumps correctly; and subjects would continue their normal lifestyle. The major limitations and uncontrolled variables in this study included:

1. No control over antecedent events which may have affected diabetic control at the beginning of the study.

2. No control over the knowledge and comprehension of the subjects.

3. No control over the accuracy, dependability and, compulsion of the diabetic subjects in recording events, measuring blood glucose levels, and managing the insulin infusion pump.

The relationship between diabetic control and heart disease risk in diabetic persons is a significant and important problem which requires further research. Replication of this study with a larger sample, longer control and study periods, and control of heart disease risk factors should produce more significant data results. As physicians gain more experience in managing diabetic

persons using the infusion pump, the average time to obtain good diabetic control and normal Hb Alc levels should decrease. Another area that should be studied is the compliance of diabetic persons using the infusion pump.

In conclusion, diabetic control improved significantly in five diabetic subjects while using the insulin infusion pump. The significance in this finding lies in the direct relationship between diabetic control and diabetic complications. The relationships between diabetic control and heart disease risk factors -- HDL, cholesterol, and triglyceride -- were not conclusive. Relationships between HbAlc, HDL, cholesterol, and triglyceride did not conform to the literature or expectations. This indicates that other variables were changing the heart disease risk indicators, which in turn changed the relationship between diabetic control and heart disease risk. This study should be replicated with control over these variables to establish a significant relationship between diabetic control and heart disease risk.

APPENDIX

DATA COLLECTION FORMS

Biographical Data

Subject Number _____

Family History:

Do any of your relatives have diabetes? Yes____ No____

	Relationship	Age	Age Onset	Insulin Used?
Relative with DM:				

Personal History:

Age at onset of your diabetes (yrs.) _____
Duration of diabetes (yrs.) _____
Insulin-dependent? ____yes ____ no
Duration of insulin use (yrs.) _____
Maximum insulin dose _____u/day.
Number of injections/day_____.

	Dose 1	Dose 2	Dose 3	Dose 4
Time				
Reg				
NPH				
Lente				
Ultralente				

	Yes	No
Neuropathy	___	___
Retinopathy	___	___
Renal Disease	___	___

Laboratory Results

Subject _____

	Precontrol 0	Postcontrol (6 Months)	Poststudy (9 Months)	
HbAlc				% Hgb
HDL				mg/dl
Cholesterol				mg/dl
Triglyceride				mg/dl

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